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REVIEW OF 1000 CONSECUTIVE CASES OF IRRITABLE COLON; ITS SIMULATION OF SURGICAL CONDITIONS AND TREATMENT

E. N. Collins, M. D., and H. S. Van Ordstrand, M.D.

The irritable colon syndrome would not be so important if medical management only were used in its treatment. Although it is well known that the symptoms may simulate any organic disease in the abdomen, we found in a series of 1000 consecutive cases that 302 operations had been done in 204 of the patients. In addition to presenting analyses of these cases, we shall attempt to clarify certain controversial features and to present certain principles of treatment.

The high incidence of this disorder as a cause of abdominal discomfort and pain warrants greater recognition than it has received in the past. The cases on which this report is based were observed during a period of only two years.

Definition

Irritable colon (spastic irritable bowel[1], unstable colon[2], functional bowel[3], mucous colic[4], mucous colitis[5], etc.) is considered to be a hyperirritable neuromuscular imbalance of the colon, *sufficiently severe to cause abdominal distress.* Although this condition may not shorten life, it can cause years of suffering, if not invalidism, and result in malnutrition either from the patient's elimination of essential foods in the diet, from change in gastrointestinal secretions, or from lack of absorption because of changes in motility, or a combination of various factors.

Many persons have either simple constipation or diarrhea for years without having abdominal distress. The term, "irritable colon," is *not* applied in these instances. It is true that patients having irritable colon commonly complain of constipation or diarrhea but neither may be present. In other words, this entity must be responsible for the patient's abdominal distress, regardless of bowel habits.

The symptoms may refer to any or all parts of the colon. Associated symptoms may refer to other parts of the digestive tract, if not to various parts of the body. Most commonly they shift from one part of the abdomen to another, across the lower abdomen, or are localized in the left lower quadrant. However, they may be localized in the right lower quadrant, simulating appendicitis; in the right upper quadrant, simulating cholecystitis; or in the epigastrium or left upper quadrant, simulating organic disease of the stomach or duodenum. Also, because of colonic distension in the left upper abdominal quadrant, the symptoms may be interpreted as cardiac disease. At the time of their initial visit some of our patients had a profound cardiac neurosis or diagnosis of "irritable heart" had been made.

An important feature is the fact that there is a lack of remission of symptoms since the date of their onset. In the present series the symptoms were present at least every week during a period (average) of eight years. It is well known that in true inflammatory disease of the digestive tract, such as peptic ulcer, biliary disease, acute appendicitis, or nonspecific or indeterminate ulcerative colitis, there is usually a history of complete remissions of symptoms over months if not years of time. In neoplasms of the digestive tract the relatively short continuous duration of symptoms (three to eighteen months' average in our experience) at the time the physician is first consulted, is noteworthy.

The symptoms may be related chiefly to colonic function, but there often is evidence of associated dysfunction in the small intestine or stomach, such as the hyperacidity syndrome, without the periodic remission of symptoms observed in patients having peptic ulcer.

Diagnosis

The diagnosis can accurately be made only by the process of exclusion. All the local, systemic, and reflex organic causes for colonic spasm or dysfunction must be excluded, as mentioned in Table 1[6]. As in the case of any functional disturbance, if the patient follows the prescribed management and does not obtain satisfactory results, the physician must continue to make follow-up studies to convince himself, as well as the patient, that no organic disease exists.

A comprehensive discussion pertaining to differential diagnosis is beyond the scope of this report. Renshaw[7] has presented observations which apply to many of the conditions mentioned in Table 1. It would appear that extensive examinations must be made in every instance

Table 1
IRRITABLE COLON

The diagnosis is made only by the process of exclusion.

1. Exclusion of organic disease in the colon. History, physical, including digital rectal examination. Stool, proctosigmoidoscopic, and roentgenologic examinations.
2. Exclusion of extracolonic disease, which may cause a toxic or reflex influence on the colon.
   (1) Intra-abdominal: peptic ulcer, biliary disease, tumors, gastritis, achlorhydria, pancreatic disturbances, regional enteritis or "terminal ileitis," urinary tract disease, uremia, renal colic, etc.
   (2) Extra-abdominal: systemic diseases, pulmonary disease, tuberculosis, lesions of central nervous system, syphilis, etc.
3. Deficiency states: self-restriction of foods, food faddists, sprue, pellagra, etc.
4. Endocrine: thyroid disturbances, menopause, premenstrual, etc.
5. Gastrointestinal allergy.

before a reasonable "working diagnosis" of irritable colon may be permitted. This need not apply unless the presenting symptoms refer to many parts of the body. If the patient has symptoms pertaining to the urinary tract, as well as to the colon, adequate examination of the urinary tract must, of course, precede other investigations. The presence of a urinary calculus may be the cause of reflex spasm in the colon. Disease in the colon cannot be excluded without stool, proctosigmoidoscopic, and roentgen examinations of the colon. A search for parasitic infestation is included in the stool examinations. The patient is given a saline cathartic before breakfast and reports to the bacteriologist immediately thereafter. The liquid stools are examined on a warm microscopic stage as soon as passed. Routine stools are examined for evidence of sprue and other evidence of abnormal digestion. The indication for other special examinations obviously depends on a careful analysis of the symptoms presented by the patient. The local, systemic, and reflex organic causes for colonic dysfunction must always be kept in mind.

In Table 2 is shown the types of the 302 operations done in 204 of the 1000 consecutive cases of irritable colon.

TABLE 2

IRRITABLE COLON

(1000 Consecutive Cases)

OPERATIONS: 302 in 204 patients without any change in symptoms

Appendectomy	163
Biliary tract	38
Pelvis (partial)	38
Pelvis (complete)	35
Gastrointestinal tract (for ulcers, adhesions, enteritis, etc.)	25
Genitourinary tract	3

At the time of our examination, these patients stated that they had precisely the same symptoms they had before operation. Many of the patients had had multiple operations, several as many as six. Although other indications for operations may have been present, the patients stated that their chief trouble was not relieved. As far as any patient was aware, none of the 302 operations was preceded by fever or jaundice. Partial and complete pelvic surgery is differentiated in the table only as to the degree of surgery, the complete resulting in surgical menopause.

CASE REPORTS

Case 1: A woman, aged 37, had suffered attacks of pain in the lower right abdominal quadrant over a seven-year period. She stated that the onset followed a pregnancy, at which time a chronic gaseous dyspepsia developed and she started a daily cathartic habit. Two years later an exploratory operation was done, the appendix removed, an ovarian cyst "punctured," and "cecal adhesions" freed. Subsequently there was no relief of symptoms. A second operation was per-

formed in the same region, "adhesions" freed, and a partial hysterectomy performed, again without relief of symptoms. A complete examination including urologic, as well as gastrointestinal investigation, was done but no evidence of organic disease was found. Management for irritable colon was instituted. She was observed at intervals over a period of two years and is known to have remained symptom-free at least during that period of time.

Discussions of other criteria which established the diagnosis of irritable colon in these three cases will follow.

Case 2: A 61 year old housewife had experienced attacks of nausea, vomiting, and pain in the right upper abdominal quadrant requiring hypodermic relief over a period of twenty-three years. She dated the onset of these symptoms soon after a pelvic operation, at which time a bilateral oophorectomy, right salpingectomy, appendectomy, and uterine suspension were done with subsequent menopause. She had experienced lifelong constipation with the self-use of daily cathartics.

Twenty years prior to our examination a gallbladder exploration was done (with normal findings), and three years previously a cholecystostomy was performed, both without relief of symptoms. At the time of our examination a complete urologic as well as gastrointestinal survey revealed no evidence of organic disease. Cholecystography revealed a normally functioning gallbladder, and there was no evidence of gall stones. Management for irritable colon was advised, and the patient has remained symptom-free for at least two years.

Case 3: The patient, a 49 year old housewife, was referred to the Urologic Department with a diagnosis of right kidney abnormality. She dated symptoms of right costovertebral flank pain with frequency and dysuria following an appendectomy and partial oophorectomy fourteen years previously, which incidentally had been done for chronic right lower abdominal pain, with no relief of symptoms. She described the right flank pain often as radiating to the right groin with vaginismus. Multiple dilatations of the right ureter had been done without relief.

Complete investigations revealed no evidence of organic disease. It was then found that she had symptoms referable to an irritable colon and the management instituted has resulted in relief of symptoms for a period of at least two years.

To show that the *initial evaluation* of the patient's symptoms and findings on physical examination are not sufficient to make an accurate diagnosis, our impressions before special examinations were instituted are shown in Table 3.

TABLE 3

INITIAL IMPRESSIONS AFTER EVALUATION OF HISTORY AND PHYSICAL EXAMINATION

Ulcer syndrome	198
Biliary disease	196
Appendiceal disease	109
Renal disease (colic, etc.)	95
Ulcer with obstruction	68
Cardiovascular disease	65
Chronic pelvic inflammatory disease	35
Diverticulitis	35
Symptoms suggesting irritable colon	199

The characteristic symptoms and physical findings of irritable colon were present in only 20 per cent; that is, 199 cases before special examinations were instituted to exclude organic disease. When patients are treated on the basis of irritable colon without adequate examination, an organic basis for the colonic symptoms may be found later. The presence of a neoplasm in the colon or a urinary calculus may be obvious then. This, of course, means that time has been lost in correcting the cause, as well as the fact that ineffective treatment has been used.

The ages of these individuals at the time the symptoms began and when first seen at the Clinic are shown in Table 4.

TABLE 4

	Age at Time Symptoms Began	*Age When First Seen at Clinic*
1-10 years	4	3
11-20 years	74	12
21-30 years	341	145
31-40 years	344	252
41-50 years	176	368
51-60 years	50	163
61-70 years	10	54
71-80 years	1	3

The average duration of symptoms and the sex distribution are shown in Table 5.

TABLE 5

AVERAGE DURATION OF SYMPTOMS:	
8 years	
DISTRIBUTION AS TO SEX:	
Females	591 or 59.1%
Males	409 or 40.9%

The possible *locations* of the abdominal distress has been mentioned. In this group of cases the average *duration* of symptoms was found to be eight years. There usually is no prolonged remission of symptoms which is commonly observed in patients having true inflammatory disease of the colon of this duration. The symptoms are more or less constant from the time of onset and vary in intensity *according to the etiologic factors involved*. The pain may be so severe that narcotics are used for relief, and in these instances we are reminded of the "green-apple colic" of boyhood days, or of patients having chronic ulcerative colitis. At least 31 of the patients in this series were known to have received hypodermic injections of various opiates.

In patients having *severe* distress, its character is usually a cramp-like pain across the lower abdomen, either relieved or intensified temporarily by having a bowel movement or by using an enema. It usually is associated with colonic function or the "passage of gas by rectum." The same features may apply regardless of the location of the distress, but in patients having *localized* distress they apply most commonly to those having distress either in the *upper* or *lower left* abdomen. In the latter group there were 161 patients who also complained of pain in the back (in the region of the lumbosacral spine) at the time of their abdominal distress, which was definitely associated with bowel function.

In patients having *mild* distress the most common complaint is a feeling of fulness and bloating (many quote the term "like a poisoned pup") within one hour after eating (gastro-colic reflex), and they may or may not have observed a relationship with bowel function.

Patients who present symptoms localized to the *right lower* abdominal quadrant, even though appendectomy has been performed, or to the *right upper* abdominal quadrant even though cholecystectomy has been performed, may not have observed any relationship to bowel function. These patients usually believe that they have biliary disease and take bile preparations containing cathartics and saline cathartics frequently over years of time. In many instances no roentgen examination of the gallbladder or biliary tract has been made. This type of treatment obviously increases irritation of the colon and may cause reflex spasm of the sphincter of Oddi, as well as spasm in other parts of the gastrointestinal tract. Our experience[8] relative to this phase of the subject, particularly with regard to nonvisualization of the gallbladder by cholecystography in the absence of opaque gall stones, coincides with that of Wilkinson[9]. Although these roentgen findings may indicate the presence of nonopaque calculi and obstruction of the cystic duct, unless there is a clear-cut history of biliary colic or jaundice, or both, the irritable colon syndrome should receive adequate consideration. The cholecystographic findings may become normal after using bowel management. In these instances the pain or discomfort in the right abdominal quadrant or upper abdomen are more or less continuous, at least not in clear-cut attacks, over years of time, and there is other evidence of irritable colon. A "gaseous dyspepsia" *per se*, even though it refers to the upper abdomen, does not necessarily indicate disease in the biliary tract.

Physical Examination

The physical examination is important from the standpoint of exclusion. The positive findings often include a tender, rope-like sigmoid colon, regardless of the location of symptoms. A distended, somewhat tender cecum may also be palpated. At times there is tenderness along the course of the entire colon, if not a generalized abdominal tenderness.

There may be a generalized hyperesthesia. When localized, the presence of parietal abdominal neuralgia (Carnett) due to postural strain or spinal abnormalities must be considered. Tenderness due to a spastic irritable colon usually is deep and is elicited only when pressure is made directly over the colon. An associated abdominal distension may or may not be present.

Diagnostic Criteria

Certain observations which suggest a disturbance in the colon are helpful when present. They may be present in patients having either organic disease or a functional disturbance.

The times of day when the abdominal distress is likely to be worse are those times when intestinal activity is greatest, such as in the early morning hours (as in chronic ulcerative colitis) and immediately after eating, due to the gastrocolic reflex.

The distress is most marked when the stools are loose, such as after taking Epsom Salts for stool examinations, or after taking the dye used in cholecystography. Some patients with irritable colon say, "I can't take cathartics."

Temporary relief of the distress is obtained when intra-colonic or intra-abdominal tension is relieved, such as by belching, passing flatus, having a bowel movement, or expelling an enema. Occasionally the distress is worse at these times as a result of incomplete expulsion, due to spasm in the sigmoid colon. During the proctosigmoidoscopic examination unusual spasm may be seen and the patient's abdominal distress may be reproduced. During the administration of the barium enema under fluoroscopic control the suspension may be seen to pass through the various segments of the colon rapidly, as in ulcerative colitis, but its passage usually is in an interrupted fashion and accompanied by spasms. The typical abdominal distress may be reproduced as the suspension enters and may be relieved after its expulsion.

Taking a glass of cold milk will relieve abdominal distress due to peptic ulcer, but may aggravate distress due to irritable colon.

Etiology

A hypersensitive nervous system in general will react more severely than normal to all manner of stimuli, so that the symptoms referable to the colon may be only a part of a general nervous state. In a comprehensive study of 60 cases of mucous colitis, White and Jones[5] demonstrated the role of emotional tension as a precipitating factor. They state, "as a rule the symptoms are seen in persons who have labile autonomic nervous systems with concurrent cardiovascular instability, and are most pronounced in persons who are in poor athletic training." They concluded that in most instances the syndrome appears to be a

somatic response to a type of nervous tension, but a number of conditioning factors seem to play a role in the production of symptoms, such as direct irritants of the colon, including rough foods, cathartics, enemas, and coincidental colonic infections.

This is one of the disorders of civilization. It is more common in the more emotional races; among so-called "temperamental stock"; fatigue, as well as nervous stress and strain, often is provocative of attacks in susceptible persons. An upper respiratory infection often causes an acute exacerbation of symptoms.

Formerly, the syndrome of irritable colon was considered to be limited to the female sex but in recent reports this has proved untrue. In this review approximately 60 per cent of the cases were in the female sex and 40 per cent, in the male sex.

Although there are numerous hereditary, constitutional, or neurogenic factors which should receive consideration, we believe sufficient attention has not been given to local irritants of the colon. In our experience the chief etiologic factor was the use of cathartics or irritating enemas (Table 6), the discontinuance of which resulted in relief of symptoms.

TABLE 6

ETIOLOGY

CATHARTICS OR IRRITATING ENEMAS:	
445 cases	approximately 45%
NEUROGENIC:	
206 cases	approximately 20%
COMBINED:	
323 cases	approximately 32%
CONTRIBUTORY:	
Anal abnormalities	
53 cases	approximately 5%

In a study of 1000 cases of unstable colon by Jordan[10] it is instructive to note that 73 per cent gave a history of the daily or frequent use of laxatives, enemas and colonic irrigations; 38 per cent of the patients gave no history of symptoms of neurogenic origin. Jordan states, "a patient in this group can therefore be regarded as having an unstable colon because of local irritation, which, from the history of the use of laxatives and the relief obtained with the omission of all measures to produce abnormal contraction, may justly be ascribed to catharsis."

In 20 per cent of the present series of cases the etiology was purely neurogenic in origin, while in 32 per cent the cause was attributable to a combination of local irritation and neurogenic factors. Since relief of symptoms cannot be expected without eradication of the cause, we believe statistics relating to irritable colon should include the chief etiologic factor.

We routinely classify all patients having this syndrome into one of three groups, i.e., those having local irritation, those having neurogenic causes, or those having a combination of both factors. If there are important contributory or unusual causes, they are included in the diagnosis. In our indices, the phrase "irritable colon" does not occur alone; it is accompanied by the chief etiologic factor.

It is interesting to note that 72 or 7.2 per cent of the patients in this review stated that their symptoms started immediately after an operation which necessitated bed rest, 3.7 per cent after childbirth, and 2.2 per cent after enforced bed rest due to accidents or other causes. This observation is included because it is believed that any cause for bed rest may be an important factor in starting the pernicious cathartic or enema habit.

Millions of dollars are spent every year for cathartics. Although thousands of persons tolerate occasional catharsis without developing an irritable colon, excessive catharsis over years of time may cause serious dysfunction in the gastrointestinal tract which results in significant deficiency disease, to say nothing of the discomfort to the patient, in unusually sensitive individuals.

Treatment

If the patient presents questionable evidence for a surgical condition, and the need for immediate surgery has been excluded, observation of the patient while on medical management obviously is in order. Progress examinations at a later date may result in a clear-cut diagnosis.

The aim of treatment obviously is the elimination of all etiologic factors. To be successful, the treatment for irritable colon must be highly individualized, according to the severity of the distress, the type of disturbances in physiologic function, and the etiologic factors involved. When the disturbance is mild and is due to fear of organic disease or to an obvious neurogenic factor which can be eliminated, the reassurance following the thorough examination itself may result in cure.

A good prognosis can be given if the chief etiologic factor is the long-continued self-use of cathartics or irritating enemas. However, when the abdominal distress is severe and multiple etiologic factors are involved, numerous details must be considered in management.

When local irritation is an important factor, it is well to recall the normal function of the colon. Although the colon is primarily an organ of storage, a certain amount of absorption also occurs, particularly in the right colon. This absorption includes fluid, minerals, and certain vitamins. The intestinal content entering the cecum is in a fluid state, and by the time it reaches the rectum it is normally soft-formed. A cathartic irritates the colon, induces rapid transit of the stool through the colon, and results in liquid stools. When this has been a daily occurrence

over years of time the mechanism of the rectal reflex, "nature's call," may be disturbed. If the patient suddenly stops using cathartics and allows normal time for the passage of food through the digestive tract, when the residue reaches the rectum he may not be cognizant of this fact. Too much fluid may be absorbed, resulting in impaction. In these instances, re-training the rectum to a "habit time," such as in the morning after breakfast, has been helpful. Until normal rectal function returns, the passage of stool may be started by the insertion of a glycerine suppository or a small amount of water, if needed. A three-ounce soft rubber ear-bulb syringe has proved useful. A three-ounce oil retention enema may be used at night if there is a tendency to hard stools. Large enemas, as well as irritating cathartics, should not be used because both procedures over-empty the colon and interfere with the re-establishment of the normal "rhythmic" colonic function.

The nature of the illness will need to be explained to many patients, but care should be used in not centering too much attention on colonic function. This may be only a part of a general nervous state and the aim of treatment is to make the patient "colon unconscious." He should follow a well-planned program and otherwise forget the colon.

Many of these individuals have unusual nervous tension and irregular habits in general. While re-establishing normal habits, emphasis must be placed on adequate rest. A good night's sleep is important even though hypnotics may need to be used at the start of treatment. A period of complete bed-rest, mid-day rest periods, more time in bed during weekends, or a vacation may need to be arranged, according to the severity of the complaints.

Antispasmodics and mild sedation commonly are used at the start of treatment. We prefer not to use mineral oil or one of the bland bulk producers by mouth, but this may be advisable for a time, if the principles of management stated above are not used and the diet is low in residue. When a reflex hyperacidity syndrome is present, alkalies are used for symptomatic relief until bowel function returns to normal.

Diet

Patients having irritable colon who believe they are suffering from constipation commonly use high-residue diets, including much "roughage," such as bran and raw apples. They may not realize that this practice can increase a tendency to constipation by increasing spasm in the colon. If the abdominal distress is severe, the use of a non-residue or low-residue diet at the start of treatment will aid in the relief of spasm. The diet should contain no vegetables or fruit during a period of several days, but may contain considerable meat and the usual "bland" foods. With relief of symptoms, cooked vegetables and fruits are added gradually, according to tolerance, until eventually the patient is on a well-

balanced diet. Raw vegetables and fruits are more irritating than the cooked forms so the latter are added first. In most instances the patient can tolerate cooked vegetables and fruits, and with continued relief of symptoms can add raw vegetables and fruits within a period of two or three weeks. The persistence of distress with constipation usually indicates continued irritation from too much bulk rather than too little.

In patients having mild distress the residue in the diet is adjusted according to bowel function. If the patient is having loose stools, a diet low in residue obviously is indicated. When the history pertaining to diet reveals a lack of essential foods, such as those containing the vitamin B complex and vitamin C, the deficiency must be overcome by using the appropriate vitamin concentrates. If there is a question of absorption from the digestive tract these vitamins should be given parenterally.

When the chief etiologic factor is neurogenic in origin the diet may be of secondary importance. However, the importance of using a well-balanced diet should be emphasized at all times.

Hospital Management

In moderately severe or severe cases of irritable colon, hospitalization is advisable. The details of strict management can be supervised and daily observations will determine the most effective treatment. The three R's of basic therapy, reassurance, relaxation, and re-education[2], can be enforced. Daily stool examinations furnish evidence pertaining to digestion. Rest and change of environment are important. While the patient is being relieved of symptoms he is taught how to manage his problem. These principles of treatment have proved as significant in this disorder as they have in other conditions, such as diabetes.

Summary

1. In a series of 1000 cases of irritable colon, 320 abdominal operations had been done in 204 of the patients, without relief of symptoms.

2. This review confirms the observations of many other clinicians, namely, that irritable colon is a common and important cause of chronic indigestion, and that it has not received the recognition it deserves.

3. The diagnosis can be made accurately only by the process of exclusion. All of the local, systemic, and reflex organic causes for colonic spasm or dysfunction must receive adequate consideration. This involves appraisal of all systems of the body when no obvious etiologic factors are present. More time and clinical judgment are required here than in the case having evidence of local colonic disease or organic abnormality in other parts of the digestive tract.

4. The most common single etiologic factor was the use of cathartics or irritating enemas; 445 cases, or 45 per cent of the 1000 consecutive cases presented this factor.

5. The symptoms and their duration, diagnostic criteria, and the type of treatment which proved most effective are included in this report.

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A NOTE ON THE EFFECT OF CERTAIN ANDROGENS UPON THE RED BLOOD CELL COUNT AND UPON THE GLUCOSE TOLERANCE*

E. PERRY MCCULLAGH, M.D. and REID JONES, M.D.

As experience with the clinical use of potent androgens accumulates, it becomes more apparent that many effects occur which are not limited to the masculinizing action of the drugs. Androgens are known to cause retention of water, sodium, chloride and nitrogen[1,2,3] and to increase body weight. They favor increased metabolic rate[4,5,6,7] and such an increase in basal metabolism usually is accompanied by weight gain and by relatively little shift in the blood pressure and pulse rate.

In reviewing blood counts done chiefly at random over a period of months or years during androgen therapy, we have become impressed by the increase in red cell count which occurs. Recently more systematic efforts have been made to follow the blood picture during androgen therapy for hypogonadism and a consistent rise in red cell count has been found. This seems especially definite following methyl testosterone therapy, due perhaps in some part to the fact that relatively large doses of this androgen have been used in our cases. A rise in hemoglobin and in hematocrit levels may be accompaniments.

Table 1 demonstrates changes in the basal metabolic rate, pulse rate, weight and the blood picture in a case of eunuchoidism treated over a long period of time. This patient developed severe hypogonadism following mumps at the age of 13 years and showed the typical clinical evidences of the disease. The patient was 32 years of age in 1932. The type and dose of androgen used is noted in the chart. The androtin mentioned as having been used from January 1933 to January 1938 was a urinary extract of relatively low potency. No significant increase in basal metabolism accompanied its use. The marked increase in weight is not considered to be due to the drug as it is not a consistent finding with the use of this extract in other cases. The basal metabolism rose during 1938 while the patient was receiving testosterone propionate, and fell to its pretreatment level or below between October 1939 and February 1940 during which time treatment was not given. The patient was given methyl testosterone orally during 1940 in the doses indicated. The metabolic rate rose approximately 25 per cent and had not fallen three weeks after cessation of the therapy. Thirty-six days after treatment was stopped, however, the basal metabolism was again low. The relatively slight change in pulse rate is shown. The gain in weight parallel-

*The testosterone propionate (Oreton) and the methyl testosterone (Oreton-M) used in these studies were donated through the courtesy of Dr. Max Gilbert and Dr. E. Schwenk of the Schering Corporation.

TABLE 1

Date	*Androgen Therapy in milligrams*	*Basal Metabolic Rate*	*Pulse*	*Weight*	*Red Blood Cells in Millions*	*Hemoglobin*	*Hematocrit in cc. per 100*
1932 Dec.		—24	72	160	4.16	74	39
1933 Jan.	Androtin						
Feb.		—28					
March					4.54	81	38
May					4.43	78	38
Aug.					4.01	75	34
1934 June					4.28	80	36
1935 Jan.					4.60	84	
Dec.		—27		192	4.40	91	
1937					4.20	72	
1938 Jan.	Testosterone propionate 5 mg. daily I.M.						
Mar. 1	25 mg. daily I.M.						
July 20	50 mg. daily I.M.						
Sept.					5.04	84	46
Sept. 20	25 mg. daily I.M.						
Oct. 3		—18					
Oct. 30	50 mg. daily I.M.						
Nov.					4.98	94	46
Dec. 6		—17	57	198			
1939 Feb. 8	50 mg. 3 times week I.M.						
Oct. 10	Therapy discontinued						
1940 Feb. 23	No therapy	—29	57	194			
Feb. 24	Methyl testosterone 50 mg. daily O.						
Mar. 27	100 mg. daily O.						
April 3	100 mg. daily O.	—15	69	197			
Aug.					5.31	94	48
Aug. 7	100 mg. daily O.	— 6	56	207			
Aug. 8	150 mg. daily O.						
Sept. 24	150 mg. daily O.	— 8	68	203	5.32	91	49
Nov. 6	100 mg. daily O.						
Nov. 12	Therapy discontinued	— 6	64	200	5.64	100	51
Dec. 3	No therapy	— 1	56	192	5.12	91	44
Dec. 16	No therapy				5.03	94	42
Dec. 18	No therapy	—22	76	190			
Dec. 23	No therapy	—18	58	190			

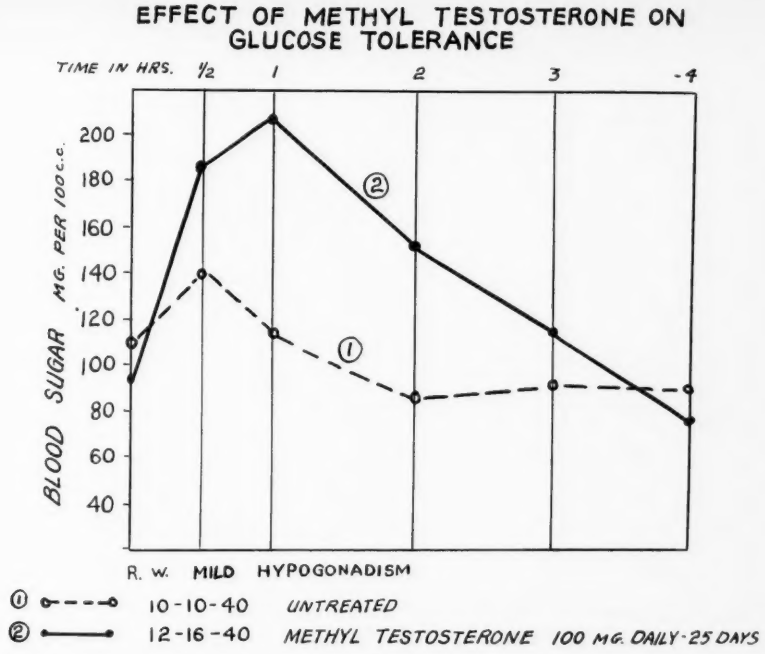

CHART I

ing the increase in the basal metabolic rate and the fall of ten to fifteen pounds on stopping treatment is typical of the effect of this drug.

This table is shown particularly to demonstrate the shift in blood count which occurred. That there should be an increase in red cell count due to androgens is not surprising if we recall that the red cell count of men is higher than that of women and children. Also, abnormally high red cell counts commonly are found in cases of adrenogenital syndrome, or Cushing's syndrome, in which there is an increase in masculinization or evidence of an excess of related steroids. This case was chosen as an example because the blood counts are spread over a long period of time, because they were all done with special care in the hematology research laboratory of Dr. Russell L. Haden and by the same technician (Miss Irene Smith) throughout. The patient was receiving relatively small doses of androgens between January 1933 and January 1938, but following January 1938 potent androgens in much larger dosages were used. Iron in various forms was prescribed from time to time prior to January 1938 but none since then. The length of time iron was used following each prescription is not shown in the records, and due to the infrequency of the blood counts the effect of the iron is not clearly apparent. The persistence of the tendency to anemia is obvious, how-

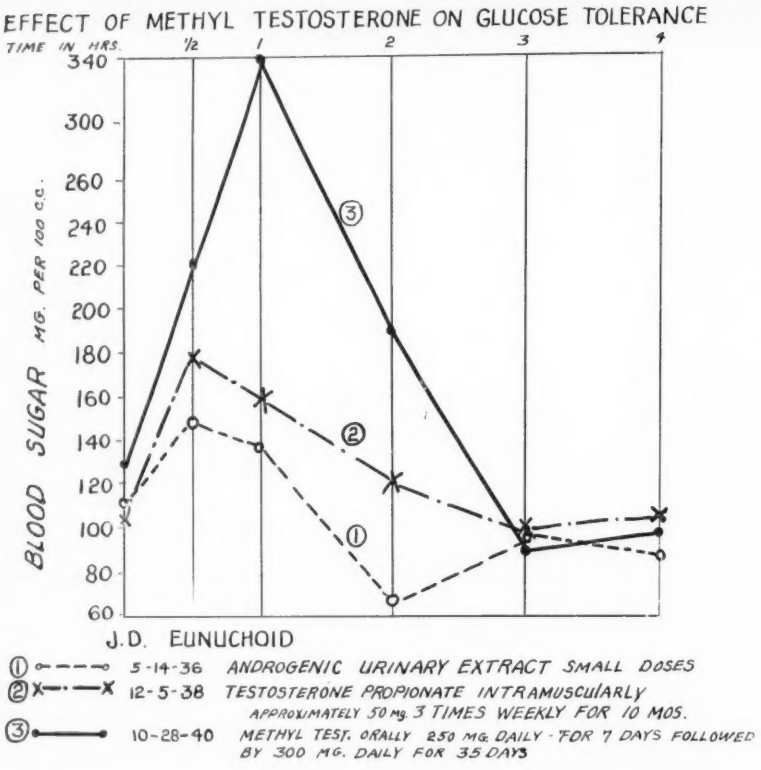

CHART II

ever. The following prescriptions for iron are shown in the records: August 1933, Blaud's mass, gr. XXX daily; October 1933, Blaud's mass, gr. XXX daily; June 1934, reduced iron; May 1937, Cupron (Ayerst, McKenna and Harrison) 3 capsules daily.

It will be seen that there was a prompt decrease in red cell count, hemoglobin and a reduction in hematocrit levels following the withdrawal of therapy in November 1940. According to our knowledge of the effect of methyl testosterone upon water retention, it seems relatively sure that the weight loss which occurred between November 12 and December 18 was due chiefly to water loss. This, if it had been responsible for a shift in red cell count, should have tended to concentrate the blood and raise the hematocrit level. Thus, it appears the more likely that the high red cell count and high hematocrit level shown on November 13 represent an actual increase in red cell mass.

Another recently observed change which has followed the use of methyl testosterone is a decrease in tolerance for glucose. It is not

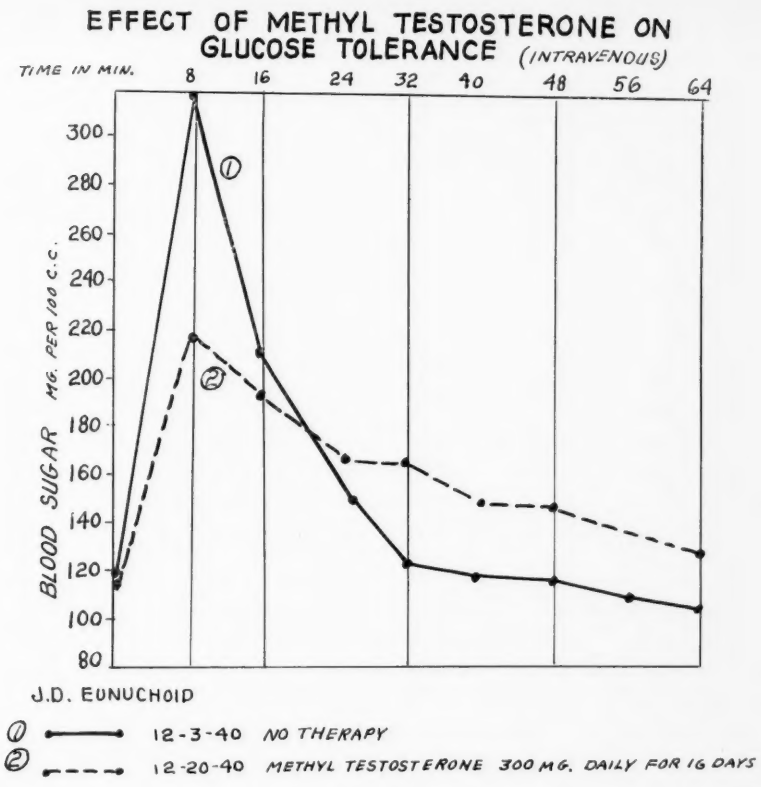

CHART III

apparent to us at this time how closely this may be related to other metabolic effects of the drug or whether it should be considered an evidence of deficiency on the part of the liver to store glucose. Liver function tests pertinent to this are being done. A decrease in tolerance following therapy or an increase in tolerance after withdrawal of therapy has been a consistent finding in 7 cases studied.

Seven glucose tolerance tests in two of the cases are shown here as examples of this change. Case W. is 19 years old and has mild hypogonadism. On November 10, 1940 prior to his using methyl testosterone a glucose tolerance test was done [labeled (1) on Chart I]. Blood sugars were estimated by Myer's[8] method, fasting, and at the intervals shown on the chart following the ingestion of 100 grams of glucose in 200 cc. of water.

The second curve, labeled (2) on Chart I, was the result of an identical

test following 100 mg. of methyl testosterone orally daily for 25 days. In Case J.D. the same type of change is shown (Chart II). The chart is self-explanatory.

In order to determine whether or not this change represented a shift in absorption rate, a glucose tolerance test was done by the intravenous method of Tunbridge and Allibone[9] (Chart III). Then therapy was stopped for seventeen days and the test repeated. "In the test described the blood sugar reading is shown to return to the preinjection level within 60 minutes in healthy young men."[9] Since the major portion of the curve is consistently higher during methyl testosterone therapy than it is following its withdrawal and since the blood sugar reading during treatment did not return to preinjection levels within sixty minutes, we assume that the shift in glucose tolerance is not due to changes in absorption and represents a failure of deposition. The fact should not be overlooked that the preceding oral glucose tolerance test was not normal and that the type of therapy which was the apparent cause of that shift had only been stopped for seventeen days before [curve (1) Chart III]. In short, if this should represent any change in liver function, judging from this test it had reverted to normal in seventeen days.

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THE PRESENT STATUS OF ROENTGEN THERAPY*

U. V. PORTMANN, M. D.

The present status of roentgen therapy depends upon many contributions to radiology by scientists in other fields. It would be impossible even to enumerate them. However, it is necessary to discuss past experiences in order to explain the rationale of modern methods of treatment.

In 1904 Bergonie and Tribondeau formulated a law which may be called the biological foundation for radium and roentgen ray treatment. They postulated, "Immature cells and cells in an active state of division are more sensitive to irradiation than are those that have acquired adult morphological and physiological characteristics." This law implies that the effect of the rays is to alter cellular functions by injury and that cells vary in their response according to their degree of differentiation in relationship to the quantity of irradiation which they absorb.

Most tissues of the body are continuously functioning and old cells are being replaced by new ones. In some tissues this takes place more rapidly than in others; therefore, normal tissues differ in the degree of their reaction to irradiation, destructibility or radiosensitivity. The same is true of pathological tissues, the cells of which, as a rule, are dividing more rapidly than those that are normal. Consequently, pathological tissues also vary in their degree of reaction to irradiation and usually are more radiosensitive than normal tissues. It is on the basis of this knowledge that in the past few years physicians have become interested in studying the histology of pathological tissues, especially tumors, to grade or classify them according to their degree of differentiation as indicative of their probable rate of growth, radiosensitivity, and curability.

The principal indications for roentgen therapy according to its biological effects are (1) to modify temporarily or to inhibit cellular functions so that physiological activities of tissues are altered, especially the secretory functions of glandular organs, and (2) to destroy pathological cells. In all probability, effects of irradiation which have been interpreted as stimulation are actually due to depression or inhibition of some functional activities of organs by cellular injury which results in or causes relative increase of other functions. It is obvious that the quantity or dose required to bring about these effects differs. Therefore, radiologists and physicists have sought ways for measuring radiation in order to apply it according to the reaction indicated, to interpret the effects upon tissue and clinical responses to treatment on the basis of known quantities administered under different and reproducible technical conditions.

In the early days of roentgen therapy, dosage was estimated by "trial

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and error" methods based upon the length of time of exposure according to voltage measured with spark-gaps and current by milliameters. The errors soon convinced radiologists that more accurate methods of determining quantity and quality of radiation were necessary in order to reproduce biological effects, especially after filters were introduced. Fluoroscopic, chemical, and photographic methods were used for some years. Soon it was apparent that the ideal method would be to measure radiation according to the actual energy of the rays, but this method has not been practical because of the difficulty of measuring such small amounts of energy. However, it has been found that the power of the rays to ionize air may be utilized to measure radiation accurately and easily. During the past fifteen years instruments have been developed for measuring ionization in air, under specified conditions, in an internationally accepted unit of quantity, the "roentgen." This unit is established by means of large open-air ionization chambers constructed according to prescribed specifications. Standard measuring apparatus of this type is available in several physical laboratories in this country, including the central one at the National Bureau of Standards in Washington, D. C.

However, large ionization chambers cannot be used by radiologists in practice. Therefore, secondary standards or "dosemeters" have been developed. These instruments are equipped with thimble-sized ionization chambers also built according to definite specifications, the most important of which being that the walls of the chamber must have a coefficient of absorption for roentgen rays approaching that of air. Dosemeters are calibrated by comparison with large standard chambers; therefore, they may be used to measure quantities of radiation independent of qualities used in roentgen therapy. In practice, radiologists may use dosemeters to determine and calibrate the roentgen output in air of their apparatus or measure the dose administered by placing the ionization chamber of the instrument directly upon the skin of patients in the field of radiation.

Dosemeters of this type also are used to measure and chart the relative difference between the quantity of radiation on the surface and that which penetrates to different depths or is absorbed. In this country, surface dose and depth absorption charts have been standardized for most of the technical conditions used in treatment; thus, radiologists now can estimate the amount of radiation administered on or in any part of the body.

However, the quantity of radiation which penetrates to different depths depends upon the quality of the rays according to voltage and filtration. Suggestions have been made for expressing quality in terms of wave-lengths determined by spectrography. But since beams of roentgen rays are not homogeneous, such terms as angstroms or minimum,

average and effective wave-length have not been acceptable to physicists. Nevertheless, radiologists require some method for defining quality and ways for determining it in practice. It is agreed that quality should be designated by "half value layer" in metals. This value is expressed as the thickness in millimeters of aluminum, copper, or lead that will absorb one-half of the quantity of a beam of roentgen rays.

It now is possible for radiologists and physicists to understand each other and to express quantity and quality of radiation in defined units, to measure and calibrate apparatus for any technical conditions according to these standards, to estimate the amount of radiation administered to any part of the body, to judge biological reactions in tissues on the basis of known quantities of radiation absorbed into them and to reproduce the physical conditions known to create certain biological effects.

In planning treatment according to the indications previously mentioned, radiologists may select the quality and the quantity of radiation that experience has proved will bring about desired effects according to the location and relative radiosensitivity of the tissues to be treated. In many instances the disease is located deep in the body, and it would be impossible to give the necessary quantity to it through a single portal of entry without damage to overlying structures. To overcome this difficulty the rays are focused at different angles upon the diseased area through several portals by what has been called "cross-fire technic," thus increasing the quantity in the region by the multiple of the number of portals used.

Although in planning roentgen therapy it is necessary to take into consideration the physical and technical factors influencing quality and quantity, it is equally important to take into account the rate of administration in relation to the rate of cellular division and multiplication in pathological tissues, especially cancers. When roentgen therapy passed the empirical stage of trial and was based upon knowledge of physical aspects, it was thought necessary in the treatment of cancer to administer in the shortest possible time as large quantities of irradiation as normal tissues could tolerate. This so-called "massive dose" technic has been supplanted in recent years by prolonged or fractionated methods with improvement in results.

The newer methods were developed when it was realized that normal tissues recover from the injurious effects of irradiation more rapidly than those that are pathologic, because abnormal cells are dividing more rapidly and are most radiosensitive in embryonic phases. In other words, more pathological cells in radiosensitive stages are affected when treatment is prolonged and there is less permanent damage to normal structures. Therefore, in administering roentgen therapy for conditions for

which large dosages are indicated, the skin tolerance is used as a basis for determining the limitations of treatment. It has been customary to use as a biological standard of dosage the quantity of radiation that, when given at one time, will result in redness or erythema of the skin in about two weeks. This reaction also varies according to quality, because the quantity of radiation absorbed and back-scattered in superficial layers is not independent of wave lengths of roentgen rays. For example, when low voltage and light filtration are used, an erythema reaction may be produced with 400 roentgens given at one time, but with higher voltage and heavier filters, 800 roentgens will be required to produce a similar reaction. However, the recovery rate of the skin from irradiation injury permits smaller doses to be given over a long period of time without serious consequences, so that the total quantity can be increased considerably in comparison with the amount that would result in skin damage if given at one time. When prolonged treatment is given in order to administer large quantities of roentgen rays, high voltage and thick filters usually are used. The daily dose customarily given to one or more skin areas may be about 250 roentgens or less. By this procedure, it is possible to administer several erythema skin doses to each area and, under certain technical conditions, from 2,000 to 4,000 or even more roentgens. Thus, the total quantity that can be delivered to tissues by this procedure is increased considerably.

Consideration of the biological effects of radiation is essential also for the regulation of dosage of roentgen rays indicated for the treatment of different types of disease. Experience has proved that modification of the secretory activities of certain glandular organs such as the pituitary gland or ovary may be influenced by very small doses of irradiation. Inflammations in many locations and diseases of the blood cell forming organs usually are treated by small or moderate dosage. Although malignant tumors vary somewhat in their radiosensitivity, they require large quantities of irradiation to destroy them, sometimes greater than can be administered without damage to normal tissues; therefore, it may be necessary to augment roentgen therapy with radium.

Many types of roentgen ray apparatus now are available, having been designed primarily to produce different qualities of radiation in sufficient quantities.

The least penetrating rays used in treatment are "Grenz" or "Borderline" rays produced at 10 kilovolts from a water cooled tube having a lithium or soda glass window. The radiation is absorbed very superficially, causes little reaction in subcutaneous tissues, and therefore, the usefulness of this type of apparatus seems to be limited to the treatment of some skin diseases.

Another type of low voltage apparatus, operating at 50 kilovolts, has

been used during the past few years for contact treatment. The apparatus was designed primarily to administer large doses of roentgen rays quickly to small superficial lesions, especially cancers, and to replace radium treatment which takes considerably longer to produce similar clinical effects. The shock-proof water or air cooled tubes are so constructed that their anode-focus to surface distance is very short, being only 18 millimeters; therefore, the radiation output is as high as 8,000 roentgens per minute without added filters and in direct contact. Filters of 1.0 or 2.5 millimeters of aluminum may be added to change the quality. Radiations of these qualities used in contact roentgen therapy also are absorbed superficially; therefore, there is little damage to tissues underlying lesions even when treated with large quantities. The tube may be introduced into body cavities or surgical openings to irradiate in locations otherwise inaccessible.

What now is called "intermediate therapy" is given at from 80 to 140 kilovolts. This type of equipment has been in use since the beginning of roentgen therapy. The quality at 80 to 100 kilovolts without filter or with a few millimeters of aluminum added is useful for the treatment of many superficial diseases and is preferred by dermatologists. When 120 to 140 kilovolts are used, the filtration is increased from 4.0 millimeters of aluminum to 0.25 millimeters of copper. Roentgen rays of this quality are generally used for the treatment of inflammations and blood diseases, but no longer are considered to be effective for treatment of malignant tumors situated deep in the body because about 90 per cent of the radiation is absorbed in the first 10 centimeters of tissue.

The demand for radiation of greater penetrability led to the development in about 1920 of "deep therapy" apparatus operating at 200 kilovolts. This type of equipment is now in general use, especially for the treatment of deeply situated diseases. Usually filters of from 0.5 to 2.0 millimeters of copper are used. The 10 centimeter depth dose with this quality is from 25 to 35 per cent of the surface dose, depending upon the filter, focus-skin distance, and the size and shape of the field of application. Thus, the total depth dose that can be administered by cross-fire methods with this quality may be equal to or greater than the surface dose.

It probably was physicists' inquisitiveness about the properties of roentgen rays approaching the quality of Gamma rays of radium and the challenge to engineers to meet their demands that has led to the development in the past few years of apparatus to operate at from 400 to 1,000 or more kilovolts. Apparatus in the 1,000 kilovolt range has been found to have certain advantages: (1) There is less back-scattered radiation to the surface because of the forward direction of the scattered

radiation and therefore better skin tolerance. (2) The greater penetrability of the rays increases the depth dose relative to surface dose to 40 or 50 per cent at 10 centimeters for 10x10 cm. portals. (3) The depth dose is relatively independent of the size of portals of entry ordinarily used in treatment, because back and lateral scattering is not great in proportion to the forward projection of the radiation. This permits many small fields to be selected to cross-fire deeply situated regions with less damage to overlying structures. (4) The radiation is heavily filtered and therefore more homogeneous than qualities produced at lower voltages, and it is more evenly distributed in tissues. Apparatus operating at voltages from 700 to 1,000 kilovolts is being used for roentgen therapy in about a dozen institutions in this country. Although not enough time has elapsed to pass final judgment about their effectiveness, reports indicate improvement over lower voltage equipment, especially for the treatment of deep-seated malignant tumors.

Neutron radiation, produced at several million volts by cyclotrons, also has been used to treat patients suffering from cancer. The impression seems to be that the reactions of normal and pathological tissues to neutron and supervoltage roentgen radiation are quite similar.

It may be mentioned at this point that during the past few years since the development of shock-proof apparatus, there has been renewed interest in the administration of roentgen therapy intra-orally and intravaginally by using suitable especially designed cones. The results indicate that in many cases this technic may be preferable to the use of radium for diseases in these locations.

The different types of apparatus now available for roentgen therapy furnish radiologists with a wide range of quality and sufficient quantity. Each has its indications and usefulness. The limitations of roentgen therapy are not attributable to physical factors, but are biological. There is no conclusive evidence that different qualities of roentgen rays have different or selective biological effects. Variations in reactions of tissues irradiated by different qualities are explainable on the basis of quantity or energy absorbed. Therefore, the voltage, filtration, and other technical factors used in roentgen therapy must be chosen according to the quantity that will be effective at the location of the lesion, and the treatment given at rates commensurate with the character of the disease and the reactions in the normal tissues which surround it.

One limitation is attributable to the fact that many pathological tissues such as low grade, slowly growing malignant tumors are little, if any, more radiosensitive than normal tissues in which they originate and grow. Under such circumstances, it may be impossible to irradiate adequately diseased areas without equal damage to normal or vital structures.

The principal limitation to treatment usually is the anatomical extent

of the disease. When pathological tissues are accessible and localized so that vital organs are not extensively involved they may be eradicated by irradiation. But unfortunately it is characteristic of cancers and allied diseases not to remain localized for very long, but to invade progressively normal structures in their neighborhood. In addition, viable cells from them may be transported in the lymph or blood streams to distant tissues where new growths or metastases develop with the same potentialities to destroy life as the parent tumor. Although primary malignant tumors may be destroyed, any secondary or metastatic growths outside of the irradiated area or in inaccessible locations could not be affected.

One of the most important problems confronting the medical profession is the treatment of cancer and allied diseases. Operations, radium, or roentgen therapy in their present status are not the final answer because of the limitations discussed. The magnitude of the problem may be

CURABILITY OF CANCER

Organ	*Relative Incidence*	*Deaths in U. S. 1931*	*Present Rate of Selected Cases (per cent)*	*5 Year Cures Average (per cent)*	*Possible Cures Under Ideal Conditions (per cent)*
Stomach	22	25,397	5	1	5
Intestine	9.4	10,953	5	2	10
Rectum	4.3	5,451	15	2	15
Uterus	12	14,464	35	10	40
Breast	9.2	11,444	33	10	35
Liver, gall bladder	8.8	10,290	2	1	5
Prostate	3.9	4,924	5	1	10
Bladder	3.1	3,874	35	15	40
Intraoral	3	3,563	25	15	50
Tongue	0.8	919	25	10	50
Lip	0.5	630	80	50	95
Pharynx	.9	1,004	5	1	25
Skin	2.5	2,986	70	60	85
Pancreas	2.5	3,139	1	?	2
Lung	2.2	2,846	.1	?	1
Esophagus	1.8	2,038	.1	?	1
Ovary	1.5	2,051	5	1	10
Kidney-adrenal	1.4	1,651	2	1	5
Bone sarcoma	1.4	1,644	5	2	10
Thyroid	1	?	2	1	5
Larynx	.8	925	20	5	50
Brain	.7	844	5	2	10
Testis	.2	345	29	5	40
Lymphosarcoma	3?	?	5	1	10

From: Treatment of Cancer and Allied Diseases, Vol. I, pp. 4-5, New York, Hoeber, Inc., 1940.

illustrated by a table compiled by James Ewing. He describes it as follows: "I have prepared the subjoined table of approximate estimates of the relative frequency of the different forms of cancer, their present rate of cure in the best clinics, the average rate of cure, and the possible rate of cure under ideal conditions. These ideal conditions include a highly educated, intelligent public, skillful and experienced specialists, and the best of modern equipment. The figures showing incidence and deaths are from the U. S. census report for 1931."

This table indicates how extensive malignant diseases usually have become by the time they are discovered or treated. Of course, no deductions can be made from it in regard to the relative roles of radiation therapy or other methods in bringing about cures. Unquestionably many patients with cancer have been cured by irradiation, but it is obvious that a vast majority must be incurable by any known procedures. Nevertheless, among the principal indications and greatest benefits of roentgen therapy is the palliation and prolongation of life and economic usefulness of people suffering from diseases that cannot be treated so successfully in any other way. Apparently it is too fantastic to hope that something will be found which, though non-toxic for normal tissues, will have selective absorption and toxicity for cancer cells or render them more radiosensitive yet. Recent investigations in the production of artificially radioactive salts and their clinical trial suggest the possibility.

Although roentgen therapy is beneficial for malignant diseases, its scope is broadening in other fields as we learn more about physiology, the etiology, and pathology of diseases, the biological effects of the rays upon tissues under controlled physical conditions, and as technics are improved. In its present status roentgen therapy is being given for many diseases, a few of which may be mentioned briefly to illustrate its applicability and effectiveness.

There is a list of almost three hundred different diseases of the skin which are amenable to roentgen therapy.

Inflammations caused by many kinds of infectious agents affecting different tissues may be benefited, pain relieved, fever reduced, and the course of the disease shortened. Such conditions as erysipelas, furuncles, carbuncles, sinusitis, mastoiditis, and inflammations of lymph glands respond very well. Gas gangrene is a serious complication of industrial and war wounds and has been the cause of many deaths but roentgen therapy, when given early, has definitely reduced the mortality rate. Although vaccines and new chemical compounds are used successfully in the treatment of some types of pneumonia, roentgen therapy also has been beneficial. Conditions such as encephalitis and inflammations of the salivary glands sometimes are due to viruses and are successfully treated in early stages. It never has been satisfactorily demonstrated that roent-

gen rays are directly germicidal in the dosages used in treatment of inflammations. It is theorized, although cooperative experimental evidence is lacking, that when infected tissues are irradiated the infiltrating phagocytes in them are destroyed so that intracellular anti-bodies are liberated to combat promptly the infectious agents.

Progress which has been made in endocrinology during the past two decades has demonstrated that roentgen therapy may modify the functional activities of glands of internal secretion, abnormalities of which are responsible for constitutional disturbances. Dysfunctions of the pituitary gland, gonads, and adrenal glands cause certain menstrual and growth disturbances which may be corrected or their progress aborted by irradiation. In this connection the treatment of uterine fibromyomas may be mentioned, which is successful in ninety per cent of properly selected cases. The symptoms of exophthalmic goiter or hyperthyroidism attributed to dysfunction of the thyroid gland may be relieved by roentgen therapy. The treatment is indicated especially when operations may be unduly hazardous or have been unsuccessful.

There are diseases of the bone marrow, spleen, and lymph glands in which blood corpuscles originate, such as myelogenous and lymphogenous leukemias, polycythemia and Hodgkins' granuloma, the causes of which are unknown. They are considered to be allied with cancer and ultimately are fatal. Roentgen therapy is the most successful treatment for relief of distressing symptoms and for prolongation of life.

The present status of roentgen therapy may be attributed to the development of many types of apparatus by ingenious engineers, to studies of the properties of radiation by meticulous physicists, to investigations of the effects upon cellular functions by inquisitive biologists and pathologists, and to the correlation and clinical application of accumulated knowledge by radiologists.

The causes of many diseases and functional disturbances are unknown; therefore, they are treated empirically and symptomatically. When the etiology of a disease is revealed, usually ways of prevention and successful treatment are developed. Future progress in medicine depends upon continued investigation and collaboration of biologists, chemists, and physicists who are familiar with clinical problems.

AN EVALUATION OF THE PHYSICAL AND MENTAL CAPABILITIES FOLLOWING REMOVAL OF THE RIGHT CEREBRAL HEMISPHERE*

LOUIS J. KARNOSH, M.D., and W. JAMES GARDNER, M.D.

DR. W. JAMES GARDNER: It has long been recognized that the loss of a considerable amount of brain tissue in the human subject may occasion surprisingly little alteration of function. Since in right-handed persons the left cerebral hemisphere is the seat of the mechanisms concerned with language, the right frontal lobe may be removed and leave the patient with little or no alteration of function. Similarly in order to accomplish the extirpation of an invasive tumor, the right temporal or occipital lobe may be removed with little disadvantage to the patient, aside from a left homonymous hemianopsia. However, the excision of the motor area and the neighboring portion of the parietal lobe results in permanent motor paralysis and profound sensory disturbances in the left half of the body.

Frequently the neurologic surgeon is confronted by a patient who has been or is about to be rendered hemiplegic by an invasive tumor near the center of the right cerebral hemisphere. Occasionally such a patient and his relatives will desire a curative rather than a palliative operation even though it means a permanent hemiplegia and homonymous hemianopsia. Because of the location of the blood supply and disposition of the nervous pathways, it is no more disabling to the patient for the surgeon to remove virtually the entire hemisphere than to attempt to excise just the midportion. This operation was described by Dandy[1] in 1928.

The purpose of this presentation is to demonstrate the physical and mental capabilities of the human subject who has had the right cerebral hemisphere removed. The material consists of four patients, the first of whom lived four and one-half years after operation, the second twenty-nine days, and the last two still are living more than two years after operation.

I will now briefly describe these four cases, after which Dr. Karnosh will describe the neurologic and mental changes produced by the extirpations.

Case 1: A woman 31 years of age complained of convulsions, weakness of the left side of the body, headaches, and failing vision†. On examination this patient was found to exhibit clonic convulsions affecting the left side of the face and neck, and occasionally the left arm. There was a left hemiparesis, a left homonymous hemianopsia, and bilateral papilledema. The clinical diagnosis was right cerebral tumor.

Operation was performed on August 31, 1931. With the patient in a sitting

*Presented at meeting of Inter-State Post Graduate Medical Association of North America, Cleveland, Ohio, October 14, 1940.

†This case has been reported previously[2,3,4].

position, a right craniotomy was performed, disclosing a large, dark, cauliflower-like tumor appearing on the surface of the brain in the temporoparietal region. The tumor infiltrated deeply beneath the surface of the brain, and it was obvious that it could not be removed totally without causing a complete left hemiplegia. After consultation with the relatives, it was decided to proceed with an excision of the hemisphere in the hope that by this procedure we could accomplish a total removal of the growth.

The emerging cerebral veins to the sagittal sinus and those from the inferior surface of the occipital lobe were ligated, cut and coagulated with the electrosurgical unit. The hemisphere was retracted laterally and an incision was made through the corpus callosum into the body of the lateral ventricle. This incision was then carried about the posterior genu and forward about the anterior genu of the corpus callosum. The branches of the anterior and posterior cerebral arteries were secured with silver clips as they were severed. An incision was made in the floor of the body of the ventricle through the internal capsule and outer portion of the corpus striatum into the descending horn of the ventricle. The hippocampal gyrus was then incised from behind forward, a considerable portion of this gyrus and a portion of the mesial wall of the temporal horn of the ventricle and choroid plexus being left. The middle cerebral artery was located, clamped about 1 cm. from its point of origin, and severed. The hemisphere was removed.

Additional brain tissue in the region of the basal ganglia which appeared to be infiltrated by the tumor was trimmed away with the electrosurgical unit. The dura was closed, the cavity filled with saline solution, the section of bone replaced, and the scalp closed.

Examination of the removed tissue disclosed a superficial portion of the tumor weighing 65 gm. The excised portion of the hemisphere weighed 520 gm. The tumor was found to have invaded the hemisphere deeply and appeared mesially at the plane of resection. Microscopically, the tumor proved to be an oligodendroglioma of a moderate degree of malignancy.

The patient's convalescence was satisfactory and she was discharged from the hospital fifty-one days after operation. This patient lived four and one-half years after operation and died following a fall down the cellar stairs. Unfortunately, permission for necropsy could not be obtained, so we cannot be certain that all of the tumor was removed.

Case 2: A woman, 25 years of age, had had symptoms of a right cerebral tumor for about a year.* Craniotomy was performed on July 9, 1934 and an infiltrating glioma of the right temporal lobe was found and a large portion of it was removed. On microscopic study, the tumor proved to be an astrocytoma. The convalescence following this operation was not satisfactory and a paralysis of the left arm occurred. After consultation with the relatives, it was decided to remove the right cerebral hemisphere in the hope of obtaining a permanent cure. Therefore, on July 17, 1934 the right cerebral hemisphere was removed as described in the previous case. This patient developed a postoperative wound infection and died twenty-nine days after operation. The surgical specimen, from which a considerable portion of the temporal lobe had been removed at the previous operation, weighed 538 grams. A postmortem examination was made which showed that the outer portion of the basal ganglia had been removed, consisting of the larger portion of the caudate nucleus, all of the putamen, about two-thirds of the globus pallidus, and a goodly portion of the anterolateral and posterior portions of the thalamus.

*This case also has been reported previously.[5].

Case 3: This case was particularly interesting because the patient was left-handed and, therefore, the speech centers were presumably in the right cerebral hemisphere. He was a man 35 years of age who had had a progressive left hemiparesis of three months' duration with jacksonian convulsions which began in the left great toe. The patient presented no symptoms or signs of increased intracranial pressure. The clinical diagnosis was a brain tumor in the right motor area. On January 31, 1938 a right craniotomy was performed. An incision through the cortex in the right premotor area disclosed a subcortical astrocytoma. No attempt was made to remove the tumor. Following this operation the paralysis of the left arm and leg was almost complete, but there was no weakness of the facial muscles and no aphasia. The patient had been left-handed since birth, he was also left-eyed and the father of the patient was left-handed, indicating that left-handedness was a familial trait, and that the right hemisphere was dominant. The patient was anxious to have the tumor completely removed even though it meant that he would have a permanent left hemiplegia. However, we were reluctant to attempt a radical extirpation of the growth because of the fear that it would leave him with an aphasia. It was decided therefore to inject novocain into the brain in an effort to determine whether the speech centers were on the right side.

Nineteen days after the first operation, a trephine opening was made in the right frontotemporal region just in front of the motor center for the face. A hypodermic needle was introduced beneath the cortex of the brain and 27 cc. of ¾ per cent novocain was injected in various directions. Following this procedure, the patient had a definite paresis of the left angle of the mouth but no

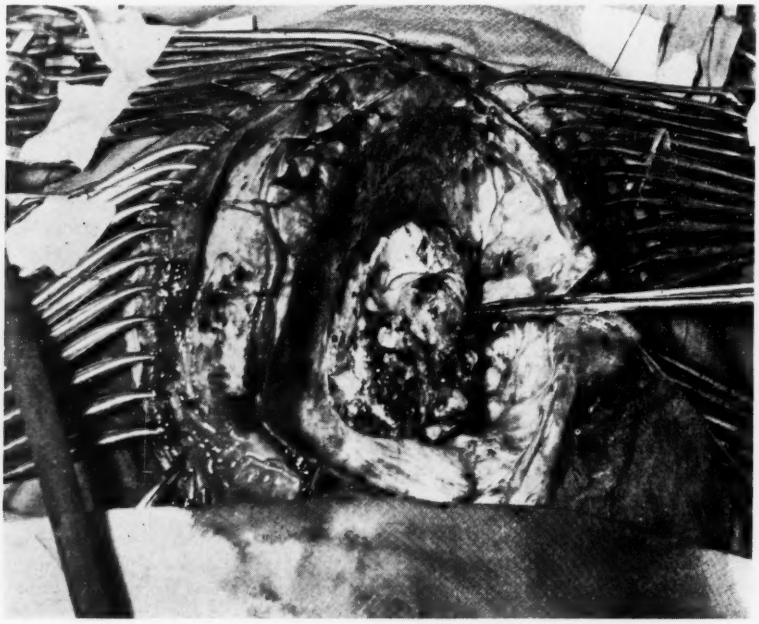

FIGURE 1 (Case 3): Photograph of the operative field after the right hemisphere had been removed, looking from behind, forward. The hemostat is on the middle cerebral artery.

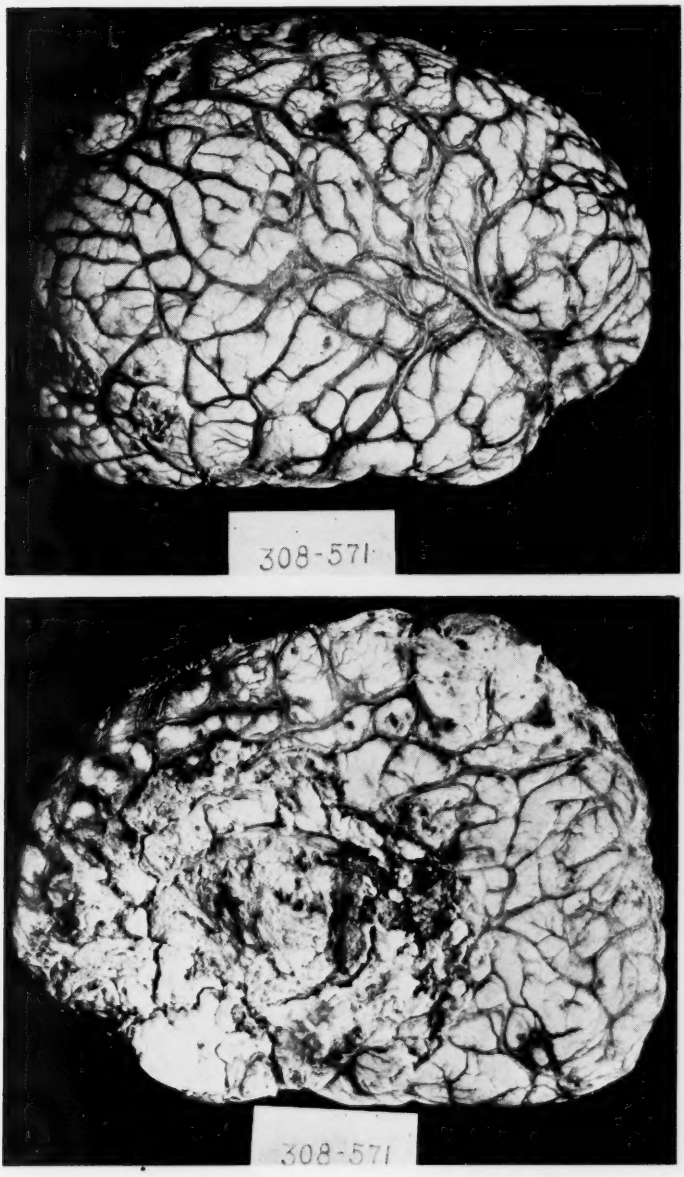

FIGURE 2 (Case 3): The surgical specimen
A. Outer surface
B. Mesial surface

FIGURE 3 (Case 3): Coronal sections. The lower right is the frontal pole and the upper left, the occipital. The cystic portion of the growth is seen clearly. The site of the novocaine injection is represented by the dark cystic area in the middle section, lower row.

aphasia was demonstrable. This we felt proved that the speech center was on the left side of the brain, even though the patient was left-handed. Accordingly, on March 3, 1938 the right cerebral hemisphere was removed with the enclosed tumor (Fig. 1). His convalescence following this procedure was satisfactory, there was no sign of aphasia, and he was discharged on the twenty-sixth post-operative day. This patient gets about well with the aid of a cane. His intellectual processes show about the same degree of impairment as has been observed in right-handed persons who have had a similar operation. Physically, however, he is less dexterous due to the fact that he has lost the use of the dominant hand. He has not yet trained himself to write with the right hand. He is still living three years after operation.

The specimen weighed 760 grams (Figs. 2 and 3). Examination showed that the entire hemisphere had been removed except for a thin layer of cortex of the medial aspect of the frontal lobe just in front of and below the anterior genu and the mesial portion of the gyrus hippocampus. The caudate nucleus, all of the putamen and a small portion of the globus pallidus were removed. The thalamus was spared. The tumor consisted of an astrocytomatous cyst in the upper parietal region with a solid portion which extended into both the frontal and the occipital lobes. There were some small cystic areas at the site where the novocain had been injected twelve days previously. The tumor apparently had been entirely removed.

Case 4: A young man of 27 years had had headaches for a year and convulsions preceded by gustatory aura for some three weeks. There were no neurological findings in his case, and no increase in the intracranial pressure.

Encephalography performed on May 14, 1938 indicated the presence of a right temporal lobe tumor. A right temporal craniotomy was performed on May

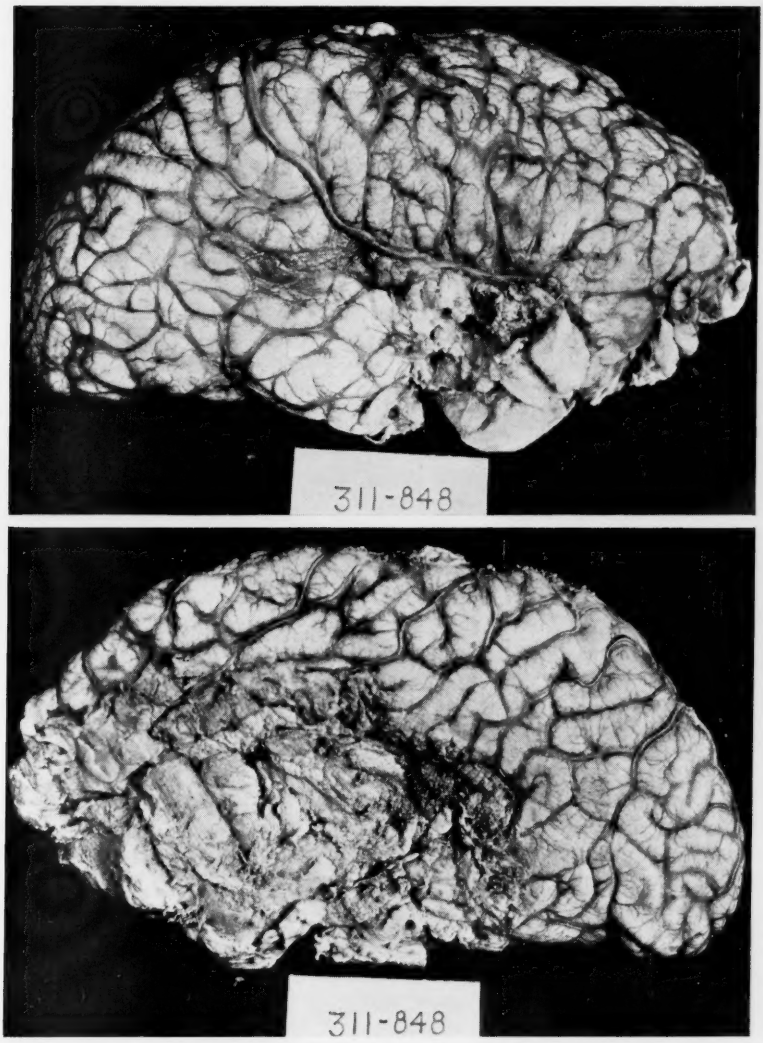

FIGURE 4 (Case 4): The surgical specimen
A. Outer surface
B. Mesial surface

22, 1938 and an astrocytoma of the tip of the right temporal lobe was found and excised. The tumor was not completely removed and during the operation the right middle cerebral artery was damaged and had to be ligated. Following this operation the patient had a left hemiplegia, but a homonymous hemianopsia was not present. The patient and his relatives were told that the tumor was not entirely removed and that a total removal of the growth would leave him with a

left homonymous hemianopsia, a complete paralysis of the left arm and a marked weakness of the left leg.

After considering the matter for six weeks, the patient returned for the radical operation. On September 7, 1938 the right cerebral hemisphere was removed as described in the preceding cases. During the operation, tumor tissue was encountered in the region of the basal ganglia so that the incision at this point was perhaps carried a little further medially than in the preceding cases. After the hemisphere had been removed, the suspicious area of the basal ganglia was treated with electrocautery in an attempt to destroy any tumor cells that might still remain. The patient's convalescence following this procedure was satisfactory, and he was discharged on the nineteenth postoperative day. He still is living two and one-half years after operation.

The specimen weighed 395 grams several months after fixation. The anterior half of the temporal lobe which was removed at the previous operation is missing from the specimen (Fig. 4). In other respects it resembled very much the specimen of the previous case. The caudate nucleus, the putamen and adjacent portions of the globus pallidus are included. The tumor extended from a point 1.5 inches behind the anterior pole, through the temporal and lower portion of the parietal lobe into the occipital lobe. It appeared that some tumor tissue may have been left in the mesial portion of the hippocampal gyrus which was spared.

DR. LOUIS J. KARNOSH: The resection of large portions of the right cerebral hemisphere for tumor is a daring and formidable procedure. If the subject survives the acute ordeals of shock, hemorrhage and infection, the clinical results at first hand are definitely consoling and are looked upon by some as something short of the miraculous. This optimism can be readily understood. The patient often comes to the neurosurgeon in semistupor, or is dulled by convulsions, headaches, blindness and maudlin mentality. These malignant symptoms generally are relieved by this operation and in this sense the contrast is striking.

The four patients presented in this discussion afforded excellent opportunity to study the end results of complete or subtotal resection of the right hemisphere. The data from one patient, however, are rather meager, for she lived only twenty-nine days after operation and satisfactory cooperation was impossible. The remaining three patients have had survival periods extending beyond two years at this time.

What manner of man or woman can be salvaged from this operation, and what the total performance of the individual may be are questions whose answers should reveal the ultimate value of the procedure. By means of periodic clinical examination, simple mental tests, moving picture records, and above all, through careful inquiries directed to relatives and friends, an attempt was made to garner the data and to formulate an intelligent answer.

The Physical Aspects

Most obvious and understandable in these four patients were the motor difficulties. Essentially this involvement consisted of a hemiplegia of the left side of the body which differs in little respect from the

orthodox picture of a paralysis following apoplexy. The left side assumed the posture which is so characteristic of a spastic paralysis. The upper extremity became flexed at the elbow, the forearm and hand were supinated, later taking on the familiar claw-like appearance. Movement in the fingers was almost nil; there was no power of movement at the shoulder joint and only with a great effort could the deformed hand be elevated toward the face. The left arm was therefore a rather useless appendage, its activity being reduced to a few crude reflexive responses.

The lower extremity was not so helpless. The thigh and knee in all instances could be extended or flexed on command although these movements were slow and clumsy. Neither ankle nor the toes could be activated and the foot was ordinarily found in a dropped position. Defense reactions in the leg were exaggerated. Despite these motor difficulties in the lower extremity, the three patients who successfully survived the operation were able to sit up, to stand and eventually to walk. Walking was possible even without the use of a cane or crutch, although this performance was somewhat awkward and frequently led to accidents. In a sitting position all three patients could elevate the defective leg and cross it over the normal extremity. The contrast between the relatively useful leg as against the distinctly useless arm and hand is demonstrated in most hemiplegias and again tends to support the general idea that the lower extremity is less dominated by the higher cortical centers than is the upper. It is almost needless to say that on the paralyzed side all reflexes were extremely exaggerated and the familiar Hoffmann and Babinski reaction usually was elicited.

Paralytic symptoms in the cranial nerves were surprisingly mild. The most striking defect was a weakness of muscle activity about the left angle of the mouth while speaking or displaying emotion. Elsewhere all facial movements were symmetrical; the brows were evenly elevated and the lids were normally raised or lowered. Ocular movements were complete in every direction.

The tongue deviated slightly to the left in one patient. The pharyngeal mechanisms were not disturbed, and chewing and swallowing presented no particular difficulty.

The function of speech as a motor performance was not radically altered in any of the three patients. In one there was noted a slight monotony of tone and a mild loss of inflection, but this was evident only in the first few weeks of the postoperative period. It already has been pointed out by Dr. Gardner that in one of our patients the speech function was demonstrated as being in the left cerebrum while handedness was found to have been in the right, or nondominant hemisphere. It is obvious that this individual was far more handicapped than the other two, for he lost the use of his more skillful hand and as a result was so helpless that he could not dress himself and all voluntary acts of his right

hand were very clumsy and tremorous performances.

More unique but less in evidence were the sensory disturbances on the paralyzed left side of these patients. There was no great subjective discomfort except a feeling of heaviness in the arm and leg. As in every spastic hemiplegia, deep pain was elicited on attempting to extend the elbow or to straighten out the spastic fingers.

Appreciation of a single stimulus with a camel's-hair brush was absent over the entire left side except on the face. Two point discrimination was equally impaired over the same area. However, if a light touch stimulus was dragged over a distance of two or three inches, it was recognized as a vague, dull pressure but its exact site could not be given. Usually the patient referred it to remote portions of the body, sometimes as much as ten or twelve inches away from the true point of stimulation. Again on the face this error was not so pronounced and the patient was able to indicate the site of stimulus with a fair degree of accuracy. This same observation was made by Dandy[6] and like him we have no adequate explanation except to say that the face or the trigeminal area may have connections with both hemispheres.

All these patients could appreciate the pain of a pinprick on the left side. It was not, however, a normal experience as compared with the right side. The prick of the pin gave rise to a very disagreeable and diffuse feeling, often interpreted as a stinging or a chilling or a burning sensation, which could not be accurately located and as one patient expressed it, "took in a large territory."

The special senses of sight, smell and hearing showed certain deficiencies, but apparently produced no great subjective discomfort in any of these patients. In all of them there was a consistent and typically left homonymous hemianopsia. Yet there was no complaint of partial blindness, and no acute inconvenience in reading. Perimetric studies explain this by showing an intact macular field in every instance.

The loss of smell could be elicited in one patient, this being on the right side and could be readily explained by the fact that the right olfactory bulb was removed in the brain resection.

There was no serious impairment of hearing except in the one individual who had the shortest survival period. This woman claimed that she could not hear in the left ear but the value of this observation is to be questioned because the patient was seriously ill with meningitis. Three patients insisted that hearing was good in both ears and this was confirmed by the audiometer in two cases.

To summarize the physical features following the removal of the right cerebral hemisphere, we present an individual who has a pronounced spastic weakness of the left arm and leg, who has little use of his upper limb but who is able to walk, who can carry out many simple

manual performances such as eating, dressing himself, writing a fair hand, and whose speech is normal. On the subjective side he is not particularly uncomfortable, although he has some difficulty in seeing objects in his left visual field and there is some blunting of fine sensation on the left side of the body.

Mental Aspects

While the physical residues in these patients could be displayed readily, the mental changes were extremely elusive. From previous reports the general impression is gained that there is very little or no psychic weakness following the operation. However, Dandy himself has some misgivings as to such negative findings. "It is still difficult," he states, "to believe that some functions of the mind are not stored or at least activated in the right hemisphere."[6]

What mental peculiarities actually existed in these patients after the resection were not readily disclosed in the routine mental tests. Actually these examinations tended at first to give the superficial impression that the subjects were quite alert, quick in reparteé and in general more vivacious than before. A more careful evaluation of this apparent animation of intellect revealed that it largely took the form of facetiousness, clowning and punning.

In none of these patients could one find any disorientation which could be called pathologic. Dates and places usually were given clearly. There was no evidence of hallucinosis or any ideas which could be called delusional.

In the matter of mood, all three patients seemed to show a definite change in the direction of wide swings in tone feeling. There was an easy trend toward dejection and moroseness with an equal tendency to mild elation and unwarranted gaiety.

The routine tests for intellectual accomplishment produced no striking abnormalities. Since accurate psychometric tests were not made of these patients before the onset of the brain tumor symptoms, no reliable comparison can be offered. The greatest difficulty lay in the inability to concentrate, to deliberate at great length and to carry out a concerted, protracted mental procedure.

The more subtle changes can only be appreciated by reviewing the behavior of these three patients as they were reimplanted upon their normal environment and as they attempted with varying degrees of success to adjust themselves to their occupations and to their social settings. The simplest way to present this phase of personality change is to give in concrete manner the story of each individual.

Case 1: The operation was done on September 23, 1931. No important mental changes were noted in the postoperative period except that she was abnormally optimistic, reacted very slowly to questions but did not seem to be

aware of this retardation. She returned to her family and after several months of wheelchair convalescence she was able to get up and carry on with some of the simpler household chores. These she did very well. The members of her family who were greatly impressed by her relative recovery were loath to admit that she had any great deviations from normal behavior. Nonetheless, they humored her in every way possible, carefully avoided direct criticism of her behavior, and lauded her greatly for any minor accomplishment. She was never asked to assume a great deal of responsibility in managing such things as the budget or in initiating any new program involving the various members of the family. She was never asked to make any major decisions. The family admitted that she was easily brought to tears, was occasionally maudlin and abnormally elated. She wrote a good letter but was inclined to repeat herself without being aware of it. The attitude of the family clearly showed that they appreciated an innate deficiency but were not willing to admit it openly. Overtures on the part of a psychiatrist to probe into her mental processes were bluntly discouraged. The patient apparently underestimated her physical handicap which was a left spastic hemiplegia. She insisted on walking about without a cane and even ventured going up and down stairs. Apparently this was the reason for her serious fall which resulted in intracranial hemorrhage and this in turn, in her death which occurred on March 6, 1936. She survived the fall by several months and during this time she become badly disoriented, showed a great loss of memory for recent events and developed periods of great excitement.

Case 3: This patient was operated upon March 3, 1938. The mental symptoms in the immediate postoperative period were simply those of emotional blunting and some mental retardation. This man had operated a small restaurant in a small town nearby. In this venture he was assisted by his wife. When he returned home from the hospital, she was greatly impressed by the improvement in his mental state, and refused at first to concede that there were any deviations from normal. She stated that he returned to his previous position, was apparently aware of his responsibility and apart from his motor helplessness there was no personality change. When it was pointed out to her that he was unusually jocular, facetious and fond of "razzing" his friends, she insisted that this was a normal trait.

However, after six months she returned with quite another story. She now admitted that his memory was spotty, that he had trouble in concentrating, and that he took no keen interest in the welfare of the restaurant business. His ability to play bridge was showing certain deficiencies. He did not seem to be greatly concerned about the financial state of affairs in the family and was inclined to dispose of serious matters with a shrug of the shoulders and with some nonsensical remark. He became more restless and seemed of abnormal gaiety despite the progressive helplessness due to the fact that his most useful hand was paralyzed.

In a more recent clinical examination his mental state clearly manifested an abnormal euphoria and considerable loss of insight into his condition. He did concede that it was difficult for him to appreciate situations about him if there was too much commotion or excitement. In attending a ball game, he could not follow all the plays and could not keep an account of the score. At the present time he is badly incapacitated by reason of his hemiplegia, cannot dress himself, eats with great difficulty and has lost all interest in his business.

Case 4: This patient was operated upon September 7, 1938 and therefore has been subject to study for a period of over two years. The immediate mental reac-

tions to the operation were not outstanding. He was moderately depressed. His speech was rather laconic and toneless, and almost immediately the content of his conversation became coarse. He became an unsavory recanteur and took delight in making sarcastic remarks about physicians and nurses.

He had been a bookkeeper prior to his illness. He has never even attempted to resume his former occupation. His relatives are very frank in stating that he is "not the same individual" and freely expressed the opinion that his personality changes are such that "he would have been better off had he not survived." The patient is not greatly disturbed by his physical handicap, is continuously punning, declines to admit his future is bad, has great ambitions but is consistently unable to carry out any program for making a living. His parents have repeatedly financed him in small schemes whereby he could earn some money. In every instance the patient started out with a great deal of enthusiasm, worked unceasingly on the project, but in a few weeks lost all interest and desire to carry on. For instance, he planned a small mail-order business, bought considerable stock, but in a few days gave up his advertising campaign. On another occasion the parents purchased some peanut-vending machines which the patient placed in three or four lucrative sites in the neighboring town. Very soon it was found that he failed to refill them. He is exceedingly unstable, inconstant, and lacks perseverance. More serious a deficiency is his utter disregard for his personal appearance. He may appear in any garb that is at hand at any time, refuses to bathe, and prefers to remain unshaved. He becomes exceedingly angry and indignant if he is reminded of his loose personal habits. Otherwise he gives the impression of being a very smart young man, somewhat bold, but keenly alive to current affairs and very clever in reparteé.

The two male patients display their personality deficiencies more prominently than does the woman. This is because more is expected of them, and they come more directly in contact with a competitive world. Even if it were not for the hemiplegia, these patients can still be regarded as failures so far as total adjustment to life's normal responsibilities is concerned.

The concept that the right hemisphere is not essential to normal mentality cannot be borne out from these studies. The operation opens a great vista to future investigation of cerebral physiology. While it may be acknowledged that the left hemisphere is vastly more important in providing the fundamental language functions of mind, from these studies it appears that the right hemisphere is also essential, particularly for the higher integrative functions such as those which deal with insight, judgment and emotional control. This phase of mind which seems to be woefully lacking in these patients may be aptly called the "long haul" in mental accomplishment and consists of those powers that provide for a normal social and moral sense and for perseverance, stability of purpose and consistence of application.

It can be concluded, therefore, that removing the right cerebral hemisphere is not comparable to removing one kidney or one lung. One cerebral hemisphere is by no means a functional replica or an understudy of the other hemisphere. An individual deprived of his non-

dominant cerebral hemisphere is no longer a normal person in his community.

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GASTROINTESTINAL ALLERGY

J. WARRICK THOMAS, M.D. and JACK KINELL, M.D.

Food allergy was noted as early as 95 B.C. Hippocrates observed, "cheese is not well tolerated by all men," and Lucretius wrote, "one man's food is another man's poison." Since that early date numerous investigators have commented upon the manifestations of allergy as related to the gastrointestinal tract. Only recently, however, has the frequency with which this association occurs been fully appreciated. In 1934, Andresen[1] reported 544 cases with gastrointestinal symptoms, 25.7 per cent of which were due to food allergy. Others do not agree with this high incidence.

Gastrointestinal allergy usually is a manifestation of food or drug hypersensitivity. Oral pollen extracts also may cause gastrointestinal symptoms. The clinical picture is variable and persons of any age may be affected. It may occur alone or in combination with other allergic manifestations or other organic pathology.

Rowe[2] lists numerous symptoms of allergic reactions in the gastrointestinal tract, such as canker sores, distention, belching, epigastric heaviness, sour stomach, pyrosis, nausea, vomiting, diarrhea, mucous colitis, constipation, "gas in the bowels," pruritis ani, pain and soreness in various sections of the abdomen, and general symptoms of instability, fatigue, and nervousness. As the symptoms are variable, a definite or characteristic clinical picture not always is observed. The indefinite symptomatology makes the diagnosis more difficult. Any of the various portions of the gastrointestinal tract may be involved and the symptoms may simulate certain acute surgical conditions. When subjected to surgery, patients with gastrointestinal allergy usually demonstrate no definite pathology. However, Osler[3] found local areas of edema in the bowel wall at operation in patients with acute abdominal angioneurotic edema.

Except for the uncommon case of definite history of reaction following the ingestion of specific foods, the diagnosis of gastrointestinal allergy still must be primarily one of exclusion. If there is evidence of an associated personal allergy or a family history of allergic disease, the supposition of a possible allergic etiology to the gastrointestinal symptoms is strengthened. Sensitization studies may yield valuable information. The proof of correct diagnosis, however, depends upon the patient's response to the program of allergy management. Such a program involves specific dietary restrictions, the avoidance of the reacting inhalant allergens and hyposensitization to these inhalants, as well as general medical supervision. It must be emphasized that simple dietary restriction alone often is not sufficient to restore the deranged physiology of the gastrointestinal tract to normal. Cooperation between the allergist

and the gastro-enterologist, with careful bowel management and specific food restriction, often is necessary before a satisfactory response to treatment is obtained. The bowel management program consists not only of the re-establishment of normal bowel physiology but also is a form of psychotherapy to relax and reassure the patient, a necessary prerogative to successful treatment in any medical problem. Complete and thorough investigation must be carried out to exclude organic disease.

The following case reports are of two patients who sought advise at the Clinic because of gastrointestinal symptoms. Both of these patients had other manifestations of allergy and in both instances, a good result was obtained by combining bowel management with a strict allergy regimen.

Case 1: A white woman, 39 years of age, complained of severe constipation, abdominal distention, gaseous dyspepsia, and nausea of eighteen years' duration. For fifteen years she had taken cathartics or enemas daily. A bowel movement gave partial relief. An appendectomy, treatment for "gastroptosis" and for disease of the gall bladder had provided no relief. Since the age of 19, she had been subject to recurrent unilateral headaches associated with nausea and vomiting. She had had chronic catarrh and nasal polypi for many years. There was no further evidence of personal or familial allergy.

General physical examination was essentially negative except for a slight pallor and edema of the nasal turbinates, and moderate tenderness in both lower quadrants of the abdomen.

A complete study of the gastrointestinal tract including roentgenographic studies, Ewald test meal, examination of the stools, and a proctoscopic examination, was entirely negative. Protein sensitization studies revealed positive reactions to many of the common inhalants as well as to several foods, including wheat and eggs.

The patient was placed on a program of rigid bowel management including allergic dietary restrictions based on the patient's history and in accordance with the findings on skin testing. She also was advised to avoid the inhalants to which she reacted. She did not follow instructions other than the avoidance of the specific inhalants mentioned. Nine months later she was unimproved. She again was placed on the original plan of management and was started on a course of hyposensitization with an extract consisting of the inhalant allergens to which she reacted. She followed instructions at this time and five months later she reported the best health she had experienced in years. The gastrointestinal symptoms, headaches and catarrh had practically cleared up. She had found that wheat definitely caused an increase in all of her symptoms.

Comment: This case, of course, is one of an irritable colon in a definitely allergic individual. A good therapeutic result was obtained by approaching the problem simultaneously from two points of view. The presence of an allergic factor in the production of the gastrointestinal symptoms seems to have been demonstrated because the patient ultimately noted an increase in symptoms after ingesting wheat.

Case 2: A 33 year old housewife complained of bowel trouble. Since childhood, she had been subject to constipation. This became more marked in the past few years, necessitating the use of frequent laxatives or enemas. For six months prior to examination she had considerable shifting, colicky, lower abdominal pain coming on about two hours after eating. During the past two

months she passed red blood and mucus with her stools. Milk and cream always increased the symptoms. Tomatoes and turnips caused excessive gas and borborygmi. She thought that paint fumes aggravated her abdominal symptoms. She had chronic catarrh, and she noticed that bromides caused a dermatitis. She also was subject to frequent hives and angioneurotic edema. Her family history was positive for allergy. One brother had hay fever and asthma, another had hay fever, and a cousin had asthma.

General physical examination revealed a moderate degree of tenderness over the cecum and the sigmoid colon, and a spastic anal sphincter with a healed fissure at the posterior commissure.

A roentgenogram of the colon was negative. Stool examinations revealed 2 plus occult blood on one occasion but subsequent examinations were negative. Proctoscopic examination revealed a melanosis of the sigmoid colon but no ulceration or other cause for the bleeding. Investigation of the urinary tract showed a moderate degree of hydronephrosis on the right which in the opinion of the examiner bore no relation to the patient's symptoms.

The patient was placed on bowel management routine and was followed for four months as an out-patient. There was slight improvement in her condition. She finally was hospitalized for two weeks for strict bowel management, section of the external anal sphincter, and for allergy investigation. Allergy studies revealed strongly positive reactions to many of the common inhalants and to many foods, including milk and wheat. Allergic dietary restrictions were incorporated into the plan of bowel management, and she was placed on a program of avoidance and hyposensitization to the inhalant allergen.

During the next six months the patient noted at least 75 per cent improvement in her gastrointestinal condition. She was almost free of hives but her nasal symptoms continued unabated. In the next three months, she had three acute attacks of abdominal pain, the last one strongly suggesting acute appendicitis. An appendectomy was performed and an acutely inflamed appendix was removed. She continued the program of management and three months later reported practically complete relief of the gastro-intestinal symptoms. She also stated that she experienced definite reactions upon attempting to liberalize her diet by adding the foods to which she reacted on skin testing. However, she was able to tolerate minimal amounts of wheat and milk. The nasal symptoms continued in spite of treatment.

Comment: This case demonstrates how complex the problem of gastrointestinal allergy may be. Bowel management alone did not control the symptoms. Organic pathology in the anus and later in the appendix were further complications. The good result in this case was obtained only by the close cooperation of the internist, the allergist, and the surgeon.

Summary

The frequency of gastrointestinal allergy has been appreciated more in recent years. Because of the multiplicity of symptoms referable to the gastrointestinal tract which may be caused by both food and drug sensitivity, the diagnosis of gastrointestinal allergy often is difficult. A strong personal or family history of atopy adds to the possibility of an allergic factor in such problems.

Although protein sensitization studies may provide valuable information, the final proof of relationship between allergy and certain gastro-

intestinal manifestations is in the response of the patient to a program of allergy management.

A thorough investigation to exclude organic disease is a necessary part of the diagnostic and therapeutic program.

The management of such problems must be shared by both the gastroenterologist and the allergist if a good result is to be obtained from treatment.

Two cases of gastrointestinal allergy which emphasize the complex character of such problems are reported in detail.

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THE HUMAN RED BLOOD CELL*

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The erythrocyte is probably the most important single cell in the animal body. It is a container for hemoglobin by which alone sufficient oxygen necessary for the life of all tissue is transported. Biologically, it is one of the most interesting of all cells. The mature erythrocyte functions as a single unit separate from all other cells; it has no nucleus during its active physiologic life; as it utilizes no oxygen, it has no metabolism of its own; it is always in motion. The red cell may be considered as an inanimate body constantly traveling from lungs to tissues and back again. It is different from every other cell.

Besides its great physiologic interest and importance, the red blood cell is remarkable because it was the first cell seen by the human eye. The first cells of any kind to be described and illustrated were those of the cork in Robert Hooke's famous "Micrographia" published in 1665.[1] Before this time, however, Swammerdam observed erythrocytes in the blood of the frog and the louse.[2] He wrote: "The same has been likewise discovered in human blood for several years, it is found to consist of ruddy globules swimming in a clear liquor." The exact date of Swammerdam's discovery is unknown but probably was as early as 1658. Malpighi[3] in 1665 mistook red blood cells for fat cells in the omentum of the hedge-hog. He described them as "fat cells looking like a rosary of red coral." Leeuwenhoek was the third of the great minute anatomists of the classical period of microscopy independently to discover the erythrocyte. On April 5, 1674, he wrote his friend Constantine Huyghens[4] that he had observed blood from his own hand with his microscope and found it to consist of "red globules floating about in a crystalline fluid." He evidently recognized the importance of his discovery as he sent a letter to the Royal Society of London only two days later containing his findings.[5] On June 1st he communicated further observations to the Royal Society. He stated that the diameter of a red globule was 1/25,000th of the grain of sand which he used as his unit of measure,[6] which corresponds to 8.5 microns. This is remarkably close to the correct figure (7.7 microns), considering the crude instrument which he used. He said that he could distinguish the corpuscles with his microscope as clearly as he could see grains of sand on black taffeta without the aid of a magnifying lens.[7] Later he thought he observed that "the sanguinous globules which made the blood red" were firmer when he was indisposed and became softer as his health was regained.[8]

With his characteristic thoroughness, Leeuwenhoek studied the red

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blood cell for many years. He examined the blood of many species of animals; found that the erythrocyte was no larger in the blood of a whale than in the smallest fish, or in the horse than in the harvest mouse; proved that the redness of the blood is due to the globules which he described; noted the variation in shape in different animals; found it to have a green rather than a red color in the grasshopper, and was the first to illustrate it (Fig. 1).[9]

2 *Experimenta & Contemplationes*

adhiberem induſtriam, ut hanc globulorum coagulationem viderem, nunquam tamen mihi contigit. Eorum tamen ortum & formationem mihi hoc pacto imaginabar; globulos nempe ex quibus farina Tritici, Hordei, Avenæ, Fagotritici, &c. conſtat, aquæ calore diſſolvi, & aquæ coadunari; hac vero aqua, quam cereviſiam vocare licet, refrigeſcente, multas ex minimis particulis in cereviſia coagulari, & hoc pacto efficere particulam ſive globulum, quæ ſexta pars eſt globuli fæcis & iterum ſex ex hiſce globulis conjungi; ut vero hanc conjunctionem mihi ob oculos ponerem, cepi 6. globulos cereos, coſque ita conjunxi, ut videre eſt Fig. 1. atque ita compoſui

fig:1. 1. 1.

& depinxi, ut ſinguli poſſent conſpici, porro conjunctos hoſce globulos ita in manibus convolvi, ut figuram acquirerent ſimilem Fig. 2. Mihi enim imaginabar, illud, quod hic convolutione inter manus efficiebam ad comprimendos globulos cereos, ex æquo fieri per agitationem cereviſiæ in comprimendis fæcis globulis, & hoc pacto fæcis globulum perfici. Nemo autem ſibi perſuadeat, me fæcis globulos ſuis circumferentiis ſeparatos vidiſſe, ut hic Fig. 2. depingitur, ſæpius enim ſex hi globuli mihi ita apparent, acſi uni bullulæ eſſent incluſi, ubi enim fæcem aquæ puræ impoſuiſſem, quia cereviſia nimis viſcoſa erat & craſſa, & hos globulos circa fundum convolvi ſiviſſem, ſex illi globuli, qui fæcis globulum conſtituunt, non a ſe invicem ſeparabantur: obſervationes hæ tam nude mihi apparebant, acſi nudo oculo videremus parvam

fig 2.

FIGURE 1: The first illustration of the red blood cell of man. From Leeuwenhoek's Arcana Natura Detecta, Delphis Batavorum, 1695, p. 2.

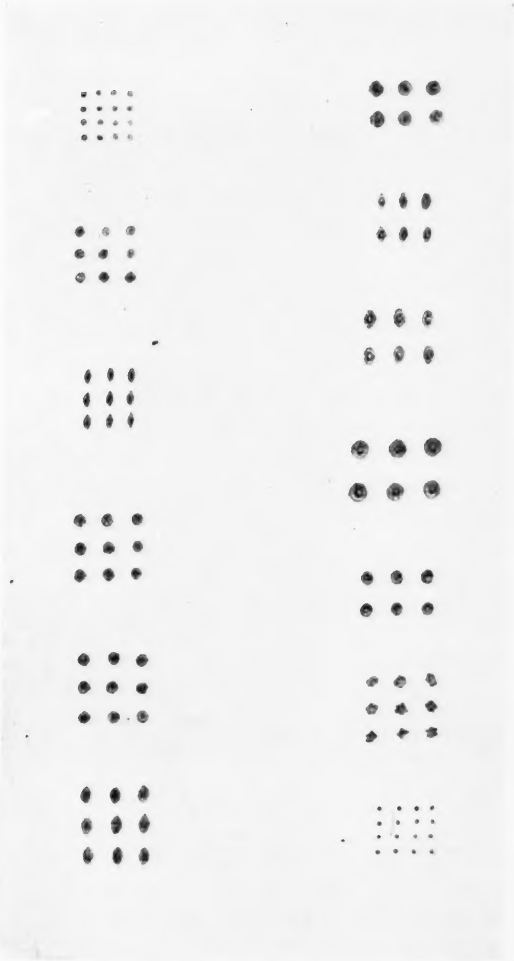


FIGURE 2: William Hewson's illustration (1773) of the red blood cell of different species. The erythrocyte of man is the second group from the top on the left. It is pictured here for the first time as a biconcave disk.

One hundred years after these early observations, William Hewson,[10] the English physiologist, presented a paper before the Royal Society of London on the "Figure and Composition of the Red Particles of the Blood Commonly Called the Red Globules." He pointed out for the first time that the red cell of man is not a globule, but a flat disk, and noted many other characteristics (Fig. 2). He wrote, "What is found so generally among animals must be of great use in their economy," although he had no idea of the function of the red cell. Even the great John

Hunter in his book on the blood[11] considered the red cell, "the least important part of the blood."

Two hundred years after the red cell was discovered, Hoppe-Seyler made his epochal studies[12] on hemoglobin in which he demonstrated that this substance readily takes up and gives off oxygen.[13] Lavoisier had shown, long before, that animal life depends upon oxidation, which is analogous to the combustion of inorganic substances, although he did not know where the oxidation of organic substances took place. It gradually became evident that oxidation occurs in the tissues and not in the lungs or circulating blood as first was supposed. Accordingly, Hoppe-Seyler's discovery provided a mechanism by which oxygen could be conveyed from the lungs to the tissues. Hemoglobin thus assumed great importance as the only means for transportation of oxygen in the body. During this period, it also was shown that hemoglobin is responsible for the red color of the corpuscle. It had been known since the time of Leeuwenhoek that the redness of blood is present only in the erythrocyte. We now have, for the first time, an explanation of the function of the red cell, a question which had puzzled Leeuwenhoek, William Hewson, John Hunter, and all other students of the blood. The tissues of the animal organism cannot live without oxygen, and can be supplied only by hemoglobin carried in the red cell. The red cell is truly a necessary and most important part of the animal economy as suspected by Hewson.

In 1851 Vierordt[14] made the first blood count and Funke discovered hemoglobin. Improvements in cell counting methods followed rapidly and numerous procedures soon were devised for measuring hemoglobin. In 1854 Welcher[15] reported the blood counts and hemoglobin estimations in many different diseases and, in 1863,[16] wrote a most complete article on the "size, the number, the volume, the surface, and the color of the blood corpuscles of man and animals." Welcher also determined the volume of the red cell in cubic microns by an indirect method long before Hedin (1890) described the hematocrit for separating red cells and plasma. Other historic landmarks in the study of the red cell are monographs by Malassez[17] on the counting of red cells (1873), by Preyer[18] on hemoglobin (1871), by Manassein[19] on the dimensions of red blood corpuscles (1872), and by Hayem[20] on the anatomy and physiology of the blood (1878). We are prone to think that finer measurements of the red cells have been made only recently. Malassez[21], however, recorded the hemoglobin in micromicrograms per cell as early as 1877. In 1881 Mrs. Ernest Hart[22] reported in man and animals the volume of the red corpuscle in cubic microns, and the corpuscular content of hemoglobin in micromicrograms. She also recorded the following measurements in various types of anemia: the hemoglobin per cm. of blood, the hemoglobin per corpuscle in micromicrograms, the number of corpuscles per milligram of hemoglobin, the

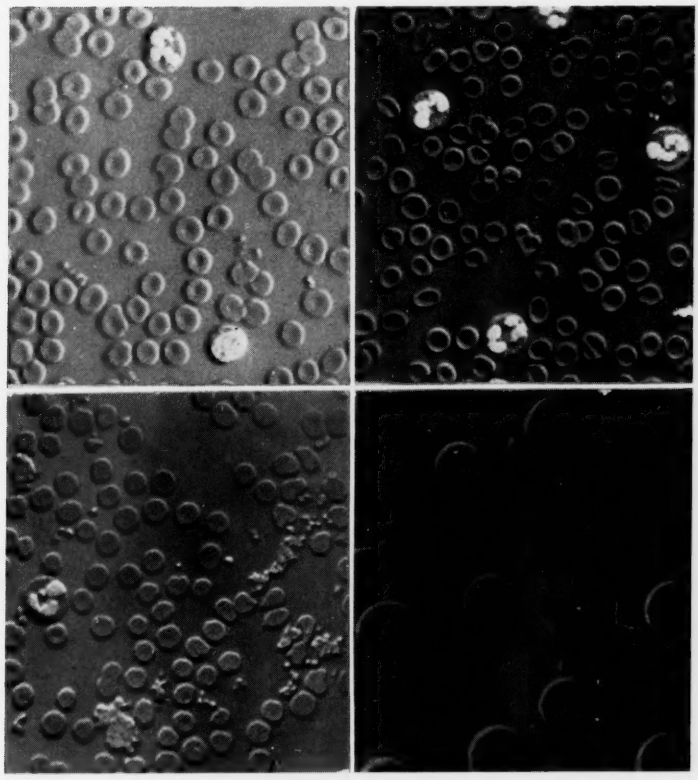


FIGURE 3: Three dimension photomicrograph of red cell. The shape of the red cell may be illustrated by bas-relief photomicrographs made by combining a positive and negative plate. The shallow, thin cells in hypochromic anemia (upper right) and the spherocytes of congenital hemolytic icterus (below) are especially well shown in relation to the normal biconcave disks (upper left).

diameter of the corpuscles, the area in square microns, and the micromicrograms of hemoglobin per unit of corpuscular substance. Certainly, no measurements of the red cell made in modern times have been more complete.

The normal erythrocyte of man is a biconcave disk varying little in volume, diameter, thickness, and hemoglobin content. The shape is best illustrated in a bas-relief photomicrograph (Fig. 3). The constancy of size and shape of the normal cell is remarkable in view of the rapid rate of red cell formation, the short span of life, and the continuous trauma to which the circulating cells are subjected. There seems to be no fixed period of life and activity for an erythrocyte. The length of time any individual cell functions seems to be determined by the chemical and mechanical injury it undergoes in the circulating blood.[23] Prob-

ably the mean span in man is about thirty days. During such a period, a red cell makes about 60,000 round trips to convey oxygen from lungs to tissues.

As the total number of cells in the circulation remains nearly constant in health, almost a trillion cells must be delivered from the bone marrow each day to compensate for those lost. Thus, new cells are produced at the rate of nearly one billion per minute.

The number, shape, size, and hemoglobin content of the red cell in the circulation depends upon numerous variables. The more important factors influencing the red cell are: (1) the condition of the bone marrow in which the cells are formed. If the amount of functioning tissue is decreased by aplasia, or replacement by other tissues as in leukemia, the normal number of new cells cannot be supplied; if the activity of the marrow is impaired by toxemia or by hypometabolism, cells cannot be formed normally. (2) The supply of specific materials necessary for making new cells. If the specific maturing principle (EMF) supplied by liver and liver substitutes is not adequate, the cell stroma cannot be formed normally; if iron is lacking, hemoglobin cannot be formed to fill the stroma. (3) The rate of destruction of red cells. The marrow attempts to compensate for a rapid destruction of cells by forming a larger number. The capacity to do this depends upon the state of the marrow and the extent of the need.

Ponder[24] thoroughly reviewed different ideas concerning the structure of the red cell. Some workers considered it a dense sponge-like body, others a bag with fluid contents. Ponder concluded[25] that the erythrocyte is a "balloon-like structure consisting of a cell membrane or envelope enclosing hemoglobin, salts, and many other substances in solution." Although a cell membrane cannot be demonstrated with the microscope, numerous studies have thrown light on its structure. It has an outer network of protein, probably only a few molecules thick. Within this are not more than four layers of lipoid, and within this is another layer of protein, intimately connected with the gel of stromatin which fills the cell interior and holds the hemoglobin (Fig. 4).

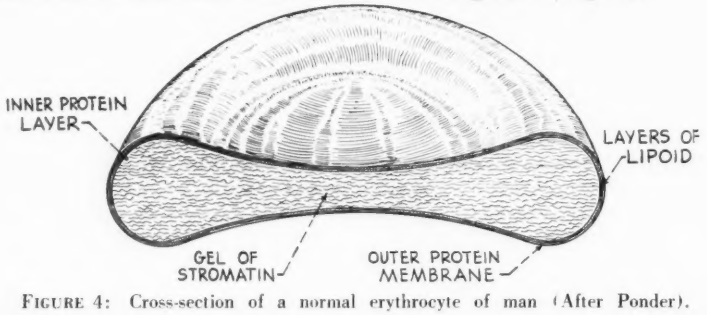


FIGURE 4: Cross-section of a normal erythrocyte of man (After Ponder).

The reason for the existence of the red cell is often overlooked. Hemoglobin is the essential element in oxygen transportation. Why should this be carried in a cell rather than in solution in the blood plasma? Barcroft[26] answered this question. As the proteins of the blood plasma cannot pass through the wall of a capillary, they exert an osmotic pressure, tending to draw water into and hold it within the lumen of the capillaries. The force of the heartbeat and hydrostatic pressure constantly tend to force fluid out of the vessels. The opposing forces are normally balanced to maintain the proper fluid relation between tissues and vessels. The normal osmotic pressure of the blood proteins is 25 to 30 mm. of water. Fifteen grams of hemoglobin, a protein, free in 100 cc. of plasma, would have an osmotic pressure of 150 mm., and would draw water from the tissues to make an impossible circulatory condition from the physical standpoint (Fig. 5). As the capillary wall is permeable by hemoglobin, smaller meshes in the wall would be necessary to hold back the hemoglobin in solution. This decreased permeability would interfere with fluid interchange between the tissues and circulating blood. Barcroft also pointed out that hemoglobin functions more efficiently in a phosphate medium and in a hydrogen concentration, such as exists in the red cell, than it would in plasma. Therefore, the efficiency of both the plasma and hemoglobin is increased by placing the hemoglobin inside the red cell "in a world all its own," and an excellent physical mechanism is provided for the necessary gaseous interchange.

The reason for the discoidal shape of the red cell is not entirely clear. The purpose of the erythrocyte is to carry the respiratory pigment, hemoglobin, which is constantly taking up and giving off oxygen. Hartridge[27] offered an explanation for the shape of the red cell in relation to this function. About 250 cc. of oxygen per minute is used by a resting man of average weight. With exercise, this may increase to 2,500 cc. per minute, and, in a day, 360 to 3,600 liters of oxygen may be used. This entire amount of oxygen in combination with hemoglobin is carried from the lungs to the tissues as oxyhemoglobin. Jacobs[28] showed that oxygen enters the red cell very rapidly. With the oxygen tension at one-third of an atmosphere, the hemoglobin in the interior of a red blood cell becomes half-saturated in one-hundredth of a second. Hartridge demonstrated that the biconcave disk is most efficient from the standpoint of gaseous diffusion. Since the structure of the red cell is like an elastic envelope containing a homogeneous matrix filled with hemoglobin, the most efficient shape for the corpuscle would allow all the contents to be saturated with oxygen in the same interval of time. In a sphere gases diffuse in at the periphery and reach the center at the same time. Also, with an infinitely thin disk, the gases reach different parts of the stratum at the same time. A sphere and a flat disk thus have the proportions required for uniform diffusion. In a sphere, however,

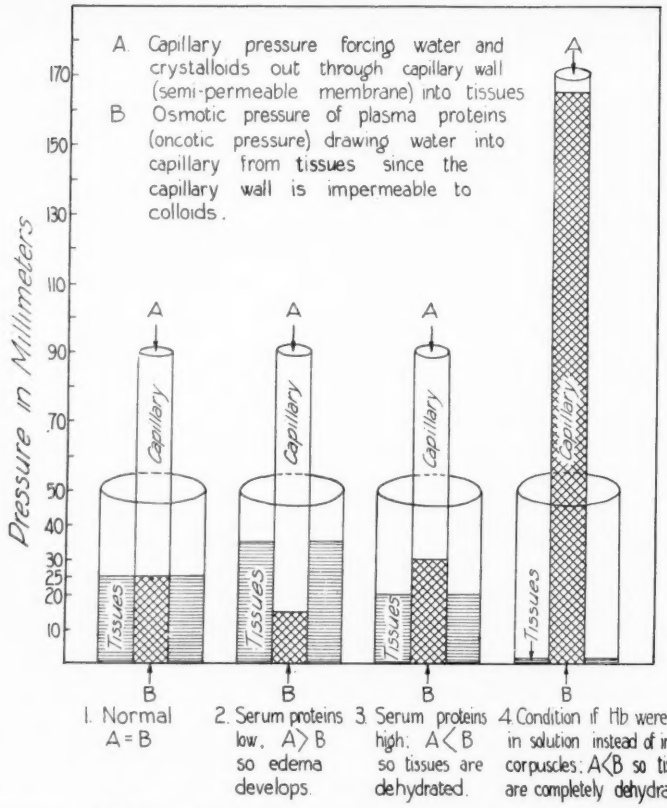

A. Capillary pressure forcing water and crystalloids out through capillary wall (semi-permeable membrane) into tissues
B. Osmotic pressure of plasma proteins (oncotic pressure) drawing water into capillary from tissues since the capillary wall is impermeable to colloids.
Pressure in Millimeters
170
150
130
110
90
70
50
40
30
25
20
10
A
Capillary
Tissues
B
1. Normal A = B
2. Serum proteins low, A > B so edema develops.
3. Serum proteins high: A < B so tissues are dehydrated.
4. Condition if Hb were in solution instead of in corpuscles: A < B so tissues are completely dehydrated.

FIGURE 5: Diagram to illustrate Barcroft's explanation of the need for a cell to carry hemoglobin in the circulating blood. The osmotic pressure exerted by the normal amount of hemoglobin (14 to 16 grams) if free in the blood plasma would draw large amounts of fluid into the vessels and so dehydrate the tissues. The hemoglobin in the red cell is outside the plasma and exerts no pressure.

the surface is small for the given bulk, and in a flat disk, the surface is increased at the expense of the contents. The biconcave disk, according to Barcroft, is a compromise between the sphere and the disk. Since the edges are thicker than the center, diffusion is uniform at any given point.

Ponder[29] does not accept this teleological explanation, but considers the discoidal form a lucky coincidence. He pointed out that the biconcave erythrocyte composed of lipoids and proteins is necessarily in a state of strain, maintained by two forces. The first tends to produce contraction and a spherical form to make a minimal surface area for the volume; the second, to produce expansion of surface area and a very flattened form. Balanced against each other, the two forces maintain the

disk shape. Ponder's concept seems to best fit the facts observed with regard to the change in shape of the red cell in response to various toxic, especially hemolytic, agents.

Since the discoidal form is maintained by a state of stress within the cell, anything which affects the structure of the surface membrane and stromatin may upset the delicate balance of the opposing forces. As the strain is released, a cell tends to become a sphere. Trauma to the cell, whether chemical, mechanical, or thermal, will alter its shape. It seems most likely, however, that the cell membrane is not elastic and cannot expand. As the stromatin and membrane, which maintain the state of strain in the corpuscle, are altered by injury, certain characteristic changes take place. These are best seen in hypotonic hemolysis, first demonstrated by Ponder and his co-workers. Using rabbit's blood,

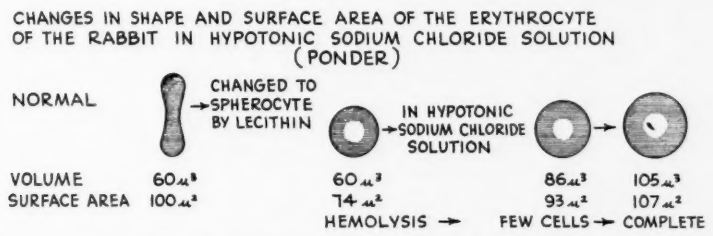


FIGURE 6: Diagram to illustrate Ponder's measurements of the erythrocyte of the rabbit as it undergoes hypotonic hemolysis.

Abramson, Furchgott, and Ponder[30] added lecithin, which affects the stroma of the cell and changes the disk to a sphere. Starting with a normal cell volume of 60 u^3 and a surface area of 100 u^2, the cell is converted into a sphere (Fig. 6). The volume is still 60 u^3 but the surface area is only 74 u^2, as it decreases with the change in shape without altering the volume. If the plasma, in which the spherical cells are suspended, is made more hypotonic the volume of the cell gradually increases. When the mean cell volume is 86 u^3 and the mean surface area is 93 u^2, hemolysis begins; when the mean volume is 105 u^3 and the surface area is 107 u^2 hemolysis is complete. From this experiment Ponder concluded that the surface of the spherical form can be stretched until it is about the same as that of the disk from which it was derived originally; if it is stretched more, the membrane breaks. This seems to prove that the membrane covering the cell cannot be stretched without breaking, although the surface membrane can contract.

One of the simplest ways to study the effect of injury on the shape of the cell is to observe a thin layer of red cells between two closely applied surfaces such as a coverglass and slide. Here spherocytes occur and various shapes are produced by changes in the cell membrane as the

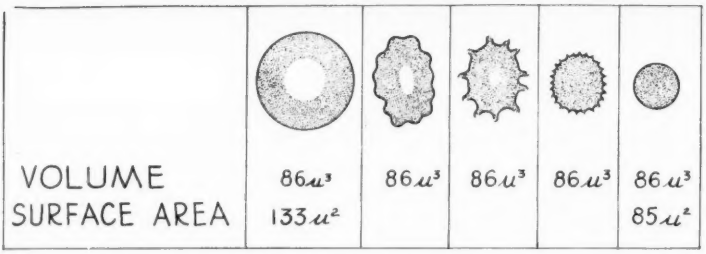


FIGURE 7: Diagram to illustrate the changes in a discoidal erythrocyte with injury. The volume is unchanged but the surface membrane first folds, then "puckers" and finally contracts to the area necessary to cover a sphere.

form is altered. First, the surface membrane folds as the surface area decreases, without change in volume; "thornapple" forms then appear. Finally, the biconcave disk becomes a sphere (Figs. 7 and 8). It seems evident that injury to the cell is followed by a loss of internal strain and a consequent alteration of the normal biconcave shape. This injury also may be produced by immune hemolysins, by hemolytic poisons such as acetylphenylhydrazine, by lysins such as bile salts and saponin, by heat, by benzene, or by toxins formed during the course of disease. The toxic agent may act on the envelope, on the lipoid fraction, or on the protein of the stromatin.

Bergenhem and Fähraeus[31] demonstrated in the spleen a substance, lysolecithin, which they think concerns the normal disposal of cells and has the property of making red cells into spherocytes. After a biconcave

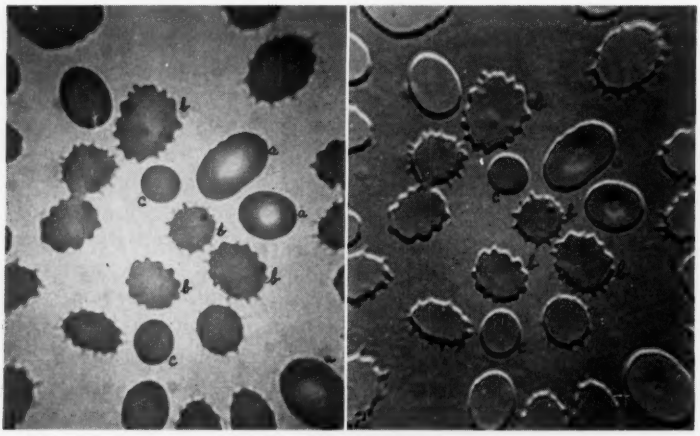


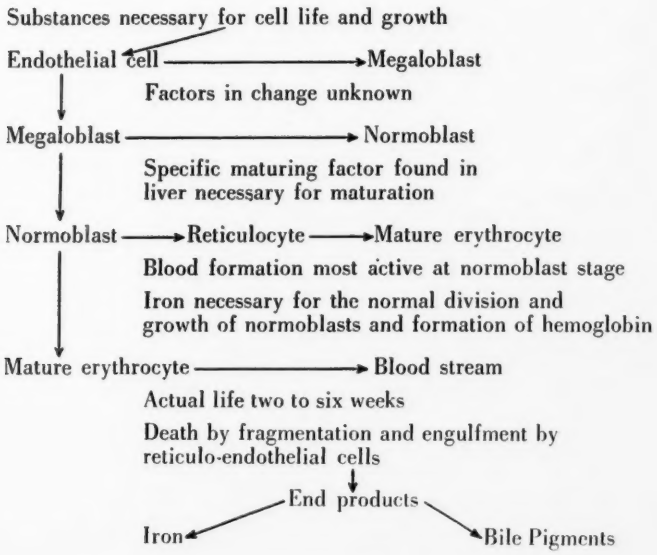
FIGURE 8: Photomicrographs of film from blood cells in the red cell mass at the bottom of an hematocrit tube after centrifuging. Note the biconcave disks (a), the crenated forms (b), and the spheres (c). The abnormal forms are shown especially well in a bas-relief photograph (2) of the same area.

disk is changed into a spherocyte, it seems to be destroyed easily so that the spherocyte may be considered a stage in the hemolysis of the erythrocyte.

Since the red cell lives only a relatively short time and is replaced by a new cell when disposed of, the life cycle is most important in relation to both normal and abnormal physiology. The normal stages of the life cycle are shown in Table 1.

TABLE 1

LIFE HISTORY OF THE ERYTHROCYTE



Certain indicators of red cell activity are necessary to evaluate the formation, circulation, and destruction of red cells (Table 3). The red cell count and the hemoglobin content record only the balance between the formation and destruction of red cells. Young red cells have the property of being stained with certain dyes. The number of reticulocytes or young cells which take the stain is an index of the rate of production of red cells ready to function in the blood stream, or at least the rate of delivery of such cells from the marrow. If the delivery of cells from the marrow is impaired, the marrow may be hyperplastic or hyperactive with a low reticulocyte count in the circulation. If the reticulocyte count in the circulation is high, the marrow is necessarily hyperplastic; if below normal, the marrow may be aplastic, hypoplastic, or hyperplastic.

When a red cell is destroyed, hemoglobin is freed, iron is split off from the hemoglobin molecule, and bilirubin is formed as the end-product of the pigment metabolism. This bilirubin is adsorbed by protein and is not excreted easily by the kidney. As the capacity of the liver cells to excrete bilirubin so formed is quickly exceeded, an excessive destruction of red cells and hemoglobin is soon reflected in an increased bile pigment content of the plasma. In the absence of biliary obstruction and liver disease, the amount of bilirubin present in the plasma indicates the rate of red cell and hemoglobin destruction. A correlation of the bilirubin content of the plasma and the reticulocyte level is shown in Table 2.

TABLE 2

RELATION OF BLOOD FORMATION AND DESTRUCTION TO BILIRUBIN AND RETICULOCYTE LEVEL

	Reticulocyte count		
Bilirubin content (icterus index)	INCREASED (over 1.5 per cent)	NORMAL (0.5-1.5 per cent)	DECREASED (under 0.5 per cent)
Increased (over 6 units)	Increased blood destruction with active bone marrow.	Increased destruction without good marrow response.	Increased destruction with inactive bone marrow or impaired delivery of red cells.
Normal (4-6 units)	Active bone marrow without excessive destruction.	Decreased marrow without excessive destruction of red cells.	Decreased formation or impaired delivery of red cells without excessive destruction.
Decreased (under 4 units)	Decreased destruction of hemoglobin due to iron deficiency; active cell formation in marrow.	Decreased destruction of hemoglobin. Decreased formation of hemoglobin; normal cell formation in marrow.	Decreased destruction of hemoglobin. Decreased formation of hemoglobin. Decreased cell formation in marrow or impaired delivery of cells.

If all the elements necessary for red cell formation are deficient, the marrow cannot make the normal number of cells at the normal rate. The marrow may function at a low speed, but such cells as are delivered to the circulation usually are normal. Two specific elements, iron and erythrocyte-maturing factor (EMF), are necessary if the marrow is to make a normal cell completely filled with hemoglobin. As the red cells develop in the bone marrow, they multiply actively at the megaloblast stage. They are not ready for delivery from the marrow, however, until completed by a substance formed by the interaction of a secretion of the stomach (the intrinsic factor of Castle) on food elements (the extrinsic factor of Castle) and stored in the liver. This substance has been designated by such names as "liver principle," the "anti-anemic principle of Castle," the "pernicious anemia principle," and "anti-megalocyte principle." As its fundamental action is to mature the red cell, or pre-

pare it for emergence from the marrow, we have designated it the erythrocyte-maturing factor (EMF). Since it is always necessary to know, in studying an anemia, whether or not there is a sufficient supply of this essential factor, there must be some indicator of its lack. The cell to which this substance (EMF) is supplied becomes smaller, so a decrease in volume of the cell is characteristic of the maturation effected by the erythrocyte-maturing factor. A macrocytosis is indicative of its lack. Although a macrocytosis usually indicates a deficiency of the erythrocyte-maturing factor (EMF), cells of increased size may be due to other causes. A hyperplastic marrow, overactive in response to a great demand for red cells, may deliver red cells larger than normal, because of rapid removal from the marrow before maturation is complete rather than a lack of erythrocyte-maturing substance (EMF). Accordingly, the hyperplastic marrow may deliver macrocytic cells in response to rapid destruction of red cells in phenylhydrazine poisoning or in spherocytic jaundice. However, in response to increased cell loss a chronic hyperplasia of marrow usually leads in time to the formation of cells smaller than normal.

Iron is the second specific element necessary for normal red cell formation. Without iron, hemoglobin cannot be formed. It is possible also that iron stimulates the growth and multiplication of red cells at the normoblast stage when division is most active. With a decrease in the amount of hemoglobin a decrease first occurs in the concentration of hemoglobin in the red cells, or in the color index. Since there is no

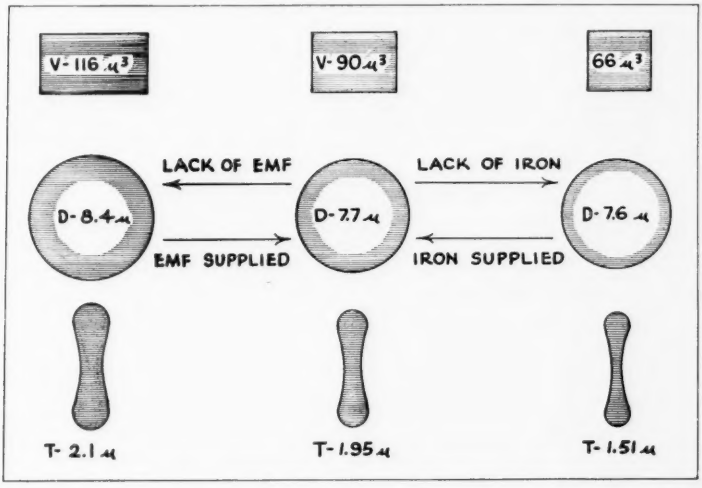


FIGURE 9: The effect of a deficiency in iron or in the erythrocyte-maturing factor (EMF) of liver on the red cell. The lack of iron produces microcytosis; iron relieves microcytosis if due to a deficiency. The lack of EMF produces a macrocytosis; liver or liver substitutes containing EMF relieve macrocytosis if due to a lack of this substance.

value in having red cell stroma without hemoglobin to fill it, and if the color index continues to be low, the cells become smaller and the volume index decreases. The hypochromia shown by the lessened color index and volume index is a measure of the lack of iron. The effect of the erythrocyte-maturing factor (EMF) and iron on the red cell are shown in figure 9.

Accurate indicators are available to show the balance between red cell formation and destruction (red cell count and hemoglobin content), the rate of destruction of red cells (icterus index), the rate of regeneration or delivery of red cells (reticulocyte count), the lack of the erythrocyte-maturing factor or EMF (macrocytosis), and a deficiency of iron (hypochromia and microcytosis) as shown in Table 3. The relation of the blood findings to red cell formation and destruction are shown in Table 4.

TABLE 3

MEASURES OF RED CELL ACTIVITY

FACTOR	INDICATOR
Balance of red cell and hemoglobin formation and destruction.	Red cell count and hemoglobin content.
Rate of destruction of red cells.	Level of bile pigment in plasma.
Rate of delivery of red cells.	Level of reticulocytes in circulation.
Deficiency of iron.	Hypochromic and microcytosis of red cells.
Deficiency of erythrocyte-maturing factor (EMF).	Macrocytosis of red cells.

TABLE 4

RELATION OF BLOOD FINDINGS TO RED CELL FORMATION AND DESTRUCTION

Active bone marrow.	Increased number of reticulocytes, basophilia, nucleation. Slight increase in mean erythrocyte volume if reticulocytosis is marked. Often an increase in leukocytes and platelets unless destruction is more active than normal. The number of cells is increased.
Inactive bone marrow.	Decrease or absence of reticulocytes, basophilia, and nucleation. If blood destruction is normal or increased, the cell count decreases.
Increased red cell and hemoglobin destruction.	Increase in bilirubin content of plasma; decrease in number of cells unless compensated for by increased marrow activity.
Decreased hemoglobin destruction.	Decrease in bilirubin content of plasma.
Deficiency in erythrocyte-maturing factor (pernicious anemia).	Anemia with increase in mean erythrocyte volume (increased volume index).
Deficiency in iron (iron deficiency anemia; chronic hemorrhagic anemia).	Anemia with hypochromia of red cells (decreased color index); microcytosis (decreased volume index) if hypochromia continues.
Hemolytic anemia.	Anemia with increased icterus index; reticulocytosis if marrow responds to increased need.
Anemia due to decrease in amount of activity of marrow (aplastic or hypoplastic anemia).	Anemia with cells of normal size and hemoglobin content; decrease in reticulocytes.

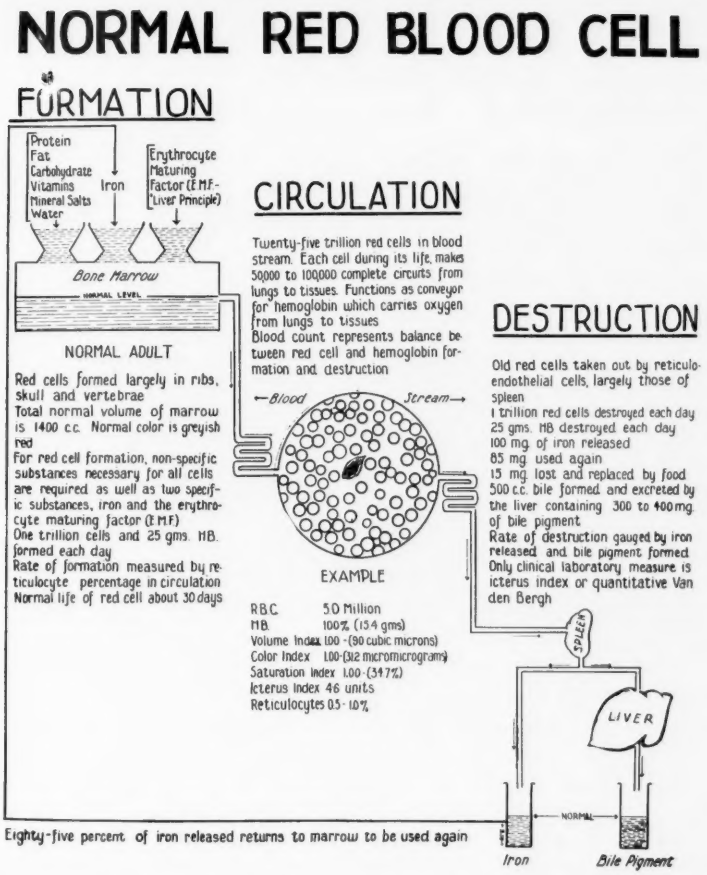

NORMAL RED BLOOD CELL
FORMATION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (E.M.F.-"Liver Principle")
Bone Marrow
NORMAL LEVEL
NORMAL ADULT
Red cells formed largely in ribs, skull and vertebrae
Total normal volume of marrow is 1400 c.c. Normal color is greyish red
For red cell formation, non-specific substances necessary for all cells are required as well as two specific substances, iron and the erythrocyte maturing factor (E.M.F.)
One trillion cells and 25 gms. HB. formed each day
Rate of formation measured by reticulocyte percentage in circulation
Normal life of red cell about 30 days
CIRCULATION
Twenty-five trillion red cells in blood stream. Each cell during its life, makes 50,000 to 100,000 complete circuits from lungs to tissues. Functions as conveyor for hemoglobin which carries oxygen from lungs to tissues
Blood count represents balance between red cell and hemoglobin formation and destruction
←Blood Stream→
EXAMPLE
RBC 5.0 Million
HB 100% (15.4 gms)
Volume Index 1.00 - (90 cubic microns)
Color Index 1.00 - (312 micromicrograms)
Saturation Index 1.00 - (34.7%)
Icterus Index 4.6 units
Reticulocytes 0.5 - 1.0%
DESTRUCTION
Old red cells taken out by reticulo-endothelial cells, largely those of spleen
1 trillion red cells destroyed each day
25 gms. HB destroyed each day
100 mg. of iron released
85 mg. used again
15 mg. lost and replaced by food
500 c.c. bile formed and excreted by the liver containing 300 to 400 mg. of bile pigment
Rate of destruction gauged by iron released and bile pigment formed
Only clinical laboratory measure is icterus index or quantitative Van den Bergh
SPLEEN
LIVER
NORMAL
Eighty-five percent of iron released returns to marrow to be used again
Iron
Bile Pigment

FIGURE 10: Normal red cell physiology. The cells are being formed and destroyed at a constant rate. The cells vary little in volume and hemoglobin content. The rate of delivery of new cells is gauged by the reticulocyte count and the rate of destruction by the icterus index. The blood count and hemoglobin content show only the balance between the formation and destruction of red cells.

The mechanism of red cell function and destruction may be illustrated by a diagram in which the bone marrow is considered as a grist mill with three hoppers supplying materials for making red cells (Fig. 10). One hopper supplies the nonspecific elements and the other two, the specific elements. Normally, the hoppers are full. The level in the mill indicates the relative fullness of the bone marrow. To maintain a normal balance between formation and destruction, nearly one trillion cells and 25 gm. of hemoglobin must be formed daily. In the circle showing the normal circulation are one hundred red cells with one

reticulocyte. The cells are of normal size and hemoglobin content. The normal findings are shown below the circle. Old red cells are taken out by the reticulo-endothelial cells, largely those of the spleen. If the blood count remains constant, as it normally does, the same number must be taken out as is delivered to the blood stream by the marrow. As the hemoglobin is destroyed, iron is split off. Some of the iron is excreted but the larger part (85 per cent) is returned to the marrow to be used again. The end-product of hemoglobin destruction is bilirubin which is excreted by the liver. The normal amount of bile pigment and iron formed is indicated by the level of these substances in the containers in which they are received. The mill is considered as functioning at a constant rate of speed to supply the same number of cells with the same hemoglobin content as is destroyed each day. The normal mean elapsed time between the release of the cell and its ultimate disposal is thirty days.

It is now possible to make very complete and very accurate measurements of the red cell. Besides the routine counts and hemoglobin estimation, the total mass of circulating erythrocytes or erythron is determined from the hematocrit reading and the total blood volume, as measured by a dye method. The mean red cell volume is calculated from the count per cu. mm. and the total red cell mass in a given amount of blood as measured with a hematocrit.[32] We have found the mean cell volume to be 90 cubic microns when using isotonic sodium oxalate (1.4 per cent) as an anti-coagulant, and centrifuging until packing is complete. The mean cell diameter may be determined in a number of ways. We have employed the Haden-Hausser erythrocytometer[33] which utilizes the principle of diffraction of light. This method is simple, accurate, and gives a normal mean cell diameter of 7.7 microns. The mean cell thickness is calculated from the volume and diameter, and the surface area from the diameter and thickness by considering the cell as a cylinder. The thickness may also be read directly from a three-dimensional chart.[34] Any unusual and abnormal shape is apparent in a stained film.

The mean hemoglobin content per cell is calculated from the red cell count per cu. mm. and the hemoglobin in grams per 100 cc. The normal figure is 30.8 micromicrograms per cell. The hemoglobin concentration per unit volume of cells is calculated by dividing the hemoglobin in 100 cc. of blood by the hematocrit reading for an equal amount of blood. The normal is 34.2 per cent which evidently is the saturation level.

The allowable variation in measurement for normal is 10 per cent. Instead of using absolute figures for cell measurements, it is very convenient to use indices to express the result in terms of normal. An index is calculated by dividing a determined figure by the normal. Thus, if the mean cell volume is 63 cubic microns, and the normal is 90, the

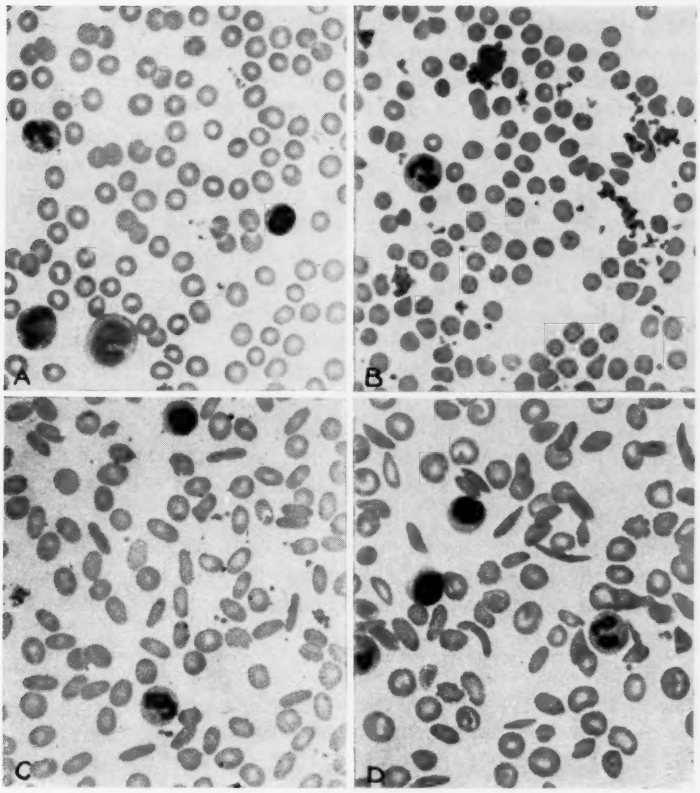


FIGURE 11: Congenital abnormality in shape and structure of the erythrocyte. A., normal biconcave disk. Note the central depression in each erythrocyte and the uniform shape and diameter. B., congenital hemolytic icterus. Note the anisocytosis with predominance of microcytes. The cells stain deeply because they are thicker than normal and have no central depression. C., oval-cell anemia. Note the predominance of oval erythrocytes. D., Sickle-cell anemia. The cytoplasm is abnormal so the cell under certain conditions became sickle-shaped.

volume index is 63/90 or 0.70. The normal measurements may be summarized:

	Mean Normal (male-wt. 70 Kg.)
Erythron	2100 cc. (30 cc. per Kg.)
Total hemoglobin	718.2 gms.
Red cells	5.0 million per cm.
Hemoglobin	15.4 gms. per 100 cc. blood
Volume of red cell	90 cubic microns
Volume index	1.00
Diameter	7.7 microns
Thickness	1.95 microns
Mean surface area	135 square microns
Mean hemoglobin content	30.8 micromicrograms
Hemoglobin (color) index	1.00
Mean hemoglobin concentration	34.2 per cent.

Certain congenital anatomic defects may affect the red cell. The cell may be congenitally globe-shaped, as in congenital hemolytic icterus, or oval shaped. The structure of the stroma may be congenitally defective also so that the cell takes on a sickle shape as in sickle-cell anemia, or may be fragile and destroyed easily as in erythroblastic anemia (Cooley's Mediterranean anemia). Cells of abnormal shape and structure are usually removed more rapidly than normal from the circulation so most such patients present an anemia (Fig. 11).

The total red cell mass or erythron has not received the attention it deserves (Fig. 12). With an anemia, the erythron may fall to a very low value. I have observed it as low as 367 cc. in a patient with idiopathic aplastic anemia. In polycythemia vera it always is increased. Here the determination of the total red cell mass helps greatly in differentiating polycythemia vera from the symptomatic type.[35] I have observed the erythron as high as 8,000 cc. in polycythemia vera. In symptomatic polycythemia the red cell mass per kilogram is not significantly increased even with a marked increase of red cells per cu. mm. of blood.

Knowledge of the size, shape, and hemoglobin content of the red cell helps greatly in the study of the anemias. By far the best laboratory classification of anemia is based on the volume and hemoglobin content

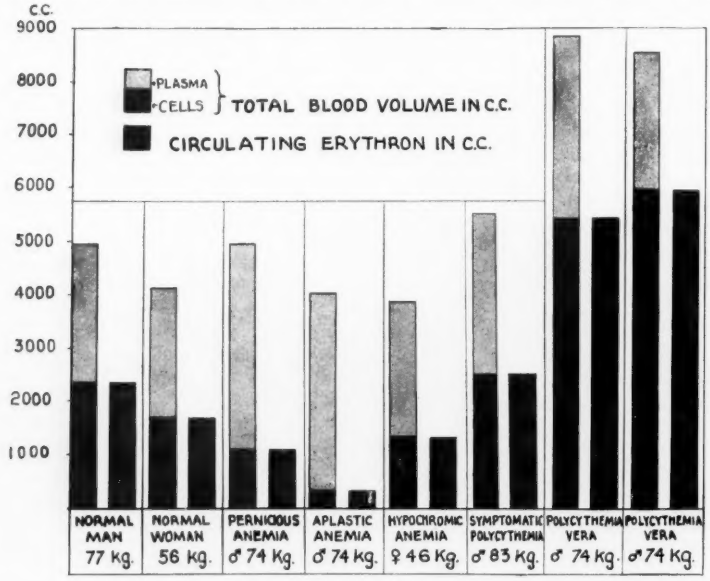


FIGURE 12: The circulating erythron varies greatly in the blood dyscrasias affecting the red cell. Here the erythron is 367 cc. in aplastic anemia and over 5,000 cc. in polycythemia vera.

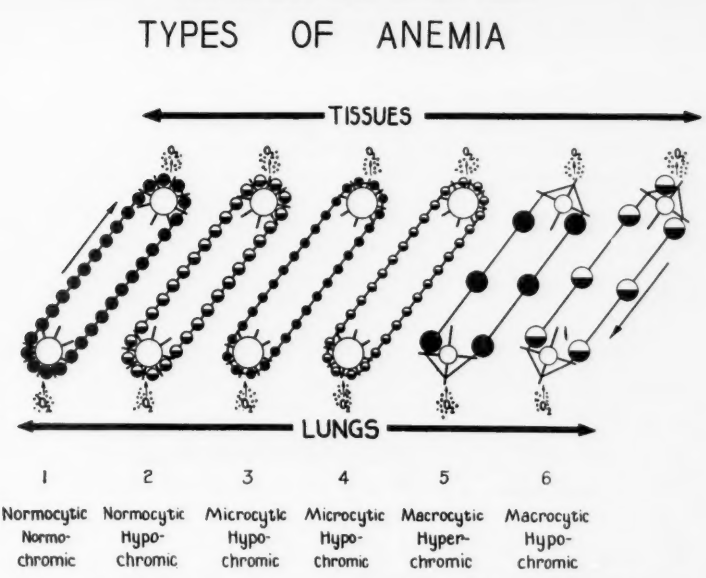


FIGURE 13: Types of anemia represented as varying kinds of endless chain conveyors. Note the great variation in volume and hemoglobin content of the cup (erythrocyte) on the chain.

of the mean red cell. While this is an objective classification it also gives the clinician clues about the cause of the anemia. Thus a microcytosis and hypochromia is never due to pernicious anemia; a hypochromia is never encountered in an iron-deficiency anemia.

The six types of anemia (Fig. 13) classified on the basis of measurements of the red cell are as follows:

1. ***Normocytic and normochromic.*** The mean cell has a normal volume and hemoglobin content. Volume index and color index, 1.00 ($\pm$ 0.10). (Fig. 13, 1)

2. ***Normocytic and hypochromic.*** The mean cell has the normal volume but is incompletely filled with hemoglobin and so has less than the normal quota. Volume index, 1.00 ($\pm$0.10), and color index, 1.00. (Fig. 13, 2)

3. ***Macrocytic and hyperchromic.*** The mean cell has a volume larger than normal and more than the normal amount of hemoglobin. Volume and color index, 1.00. (Fig. 13, 5)

4. ***Macrocytic and normochromic.*** The mean cell is larger than normal but contains a normal amount of hemoglobin although the concentration is less than normal. Volume index, 1.00, and color index, 1.00 ($\pm$ 0.10). (Fig. 13, 6)

5. ***Macrocytic and hypochromic.*** The mean cell is larger than normal and contains less than the normal quota of hemoglobin. Volume index, 1.00, and color index, 1.00. (Fig. 13, 6)

6. ***Microcytic and hypochromic.*** The mean cell is smaller than normal and contains less than the normal amount of hemoglobin. Volume and color index, 1.00. (Fig. 13, 3 and 4).

The great value of knowing the shape of the cell or at least the degree of spherocytosis in the study of hemolytic anemia is emphasized in an article on hemolytic anemia.[36] In obstructive jaundice the cells tend to be flattened. A macrocytosis may be observed in conditions other than pernicious anemia. These have already been mentioned but may be summarized:

1. Reticulocytosis from any cause as young cells tend to be larger than normal.

2. Defective absorption of the specific principle of liver (erythrocyte-maturing factor) as in chronic diarrhea or defective use as in myxedema.

3. Cellular liver disease not due to obstruction of the extrahepatic bile ducts. The macrocytosis here seems due to the inability of the liver to store or utilize the erythrocyte-maturing factor.

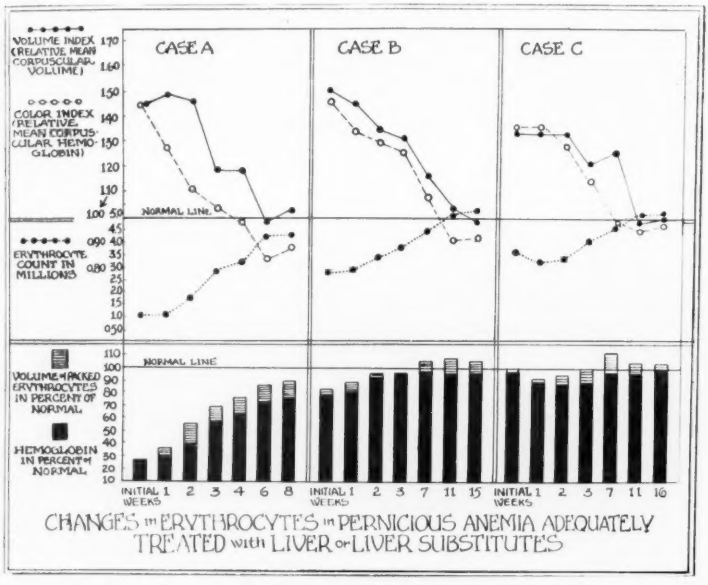
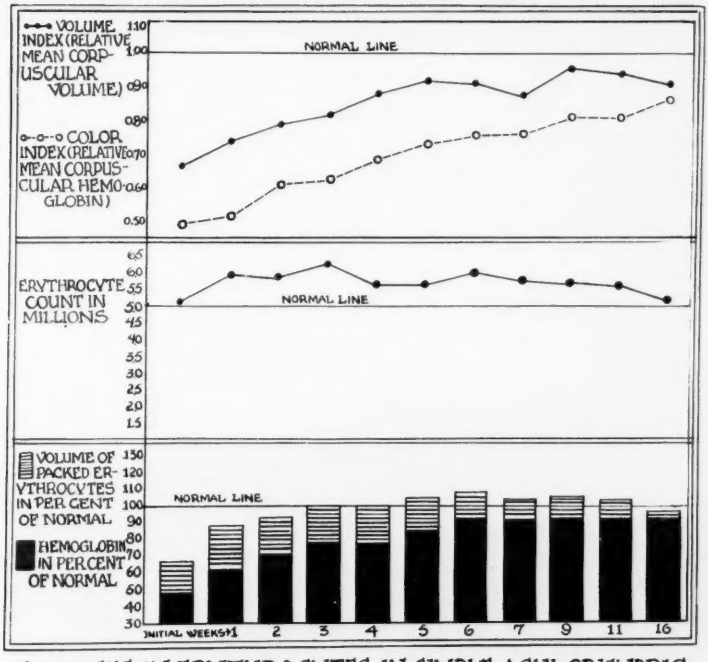

CASE A
CASE B
CASE C
VOLUME INDEX (RELATIVE MEAN CORPUSCULAR VOLUME)
COLOR INDEX (RELATIVE MEAN CORPUSCULAR HEMOGLOBIN)
NORMAL LINE
ERYTHROCYTE COUNT IN MILLIONS
VOLUME PACKED ERYTHROCYTES IN PERCENT OF NORMAL
HEMOGLOBIN IN PERCENT OF NORMAL
INITIAL 1 2 3 4 6 8 WEEKS
INITIAL 1 2 3 7 11 15 WEEKS
INITIAL 1 2 3 7 11 16 WEEKS
CHANGES IN ERYTHROCYTES IN PERNICIOUS ANEMIA ADEQUATELY TREATED WITH LIVER OR LIVER SUBSTITUTES

FIGURE 14: Changes in the red cells in pernicious anemia with adequate therapy. Note in every case the large volume of the mean erythrocyte before treatment and the return to normal with treatment. If adequate therapy is continued, the mean cell remains normal.


VOLUME INDEX (RELATIVE MEAN CORPUSCULAR VOLUME)
COLOR INDEX (RELATIVE MEAN CORPUSCULAR HEMOGLOBIN)
NORMAL LINE
ERYTHROCYTE COUNT IN MILLIONS
NORMAL LINE
VOLUME OF PACKED ERYTHROCYTES IN PER CENT OF NORMAL
HEMOGLOBIN IN PER CENT OF NORMAL
NORMAL LINE
INITIAL WEEKS 1 2 3 4 5 6 7 9 11 16

CHANGES IN ERYTHROCYTES IN SIMPLE ACHLORHYDRIC ANEMIA WITH ADEQUATE IRON THERAPY.

FIGURE 15: Changes in the red cells in a patient with iron-deficiency anemia when given adequate amounts of iron. Note the gradual increase in volume of the cell as well as hemoglobin content.

4. Idiopathic aplastic anemia nearly always shows a microcytosis of the red cells. A microcytosis or hypochromia on the other hand is seldom seen except as the result of an iron deficiency. A hypochromia has the same implication.

Knowledge of the volume of the mean red blood cell is necessary in determining the adequacy of treatment of pernicious anemia. With complete therapy the mean cell volume returns to normal (Fig. 14). Likewise in the microcytosis and hypochromia of an iron deficiency, with adequate iron therapy, the cell returns to normal (Fig. 15).

The mechanism of changes in the red cell in an anemia due to a deficient supply of the erythrocyte-maturing factor such as idiopathic pernicious anemia is illustrated in figure 16. Here the hopper supplying the specific factor is poorly filled. The marrow is red because of a great piling up of incomplete cells as shown at necropsy or by sternal puncture. The cells die in the marrow in excessive numbers without reaching

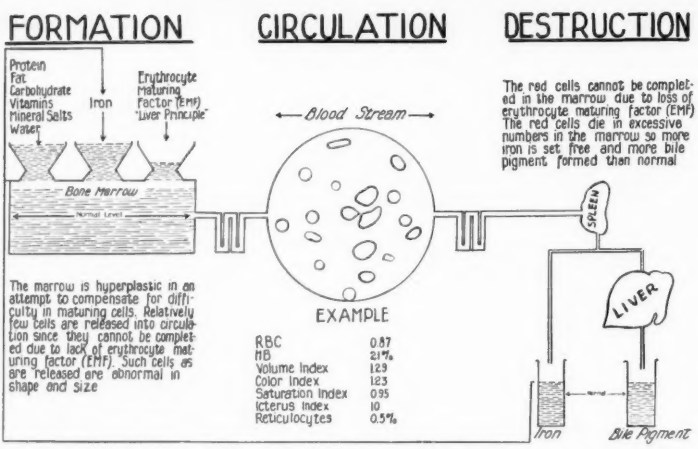

FORMATION
CIRCULATION
DESTRUCTION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (EMF) "Liver Principle"
Bone Marrow
Normal Level
Blood Stream
The red cells cannot be completed in the marrow due to loss of erythrocyte maturing factor (EMF) The red cells die in excessive numbers in the marrow so more iron is set free and more bile pigment formed than normal
SPLEEN
LIVER
The marrow is hyperplastic in an attempt to compensate for difficulty in maturing cells. Relatively few cells are released into circulation since they cannot be completed due to lack of erythrocyte maturing factor (EMF). Such cells as are released are abnormal in shape and size
EXAMPLE
RBC 0.87
HB 21%
Volume Index 1.29
Color Index 1.23
Saturation Index 0.95
Icterus Index 10
Reticulocytes 0.5%
Iron
Bile Pigment

FIGURE 16: Red cells in an anemia due to an idiopathic defect in formation of the erythrocyte-maturing factor (pernicious anemia). Here the marrow is hyperplastic because the cells cannot be completed normally and accumulate. Such cells as are released are not normal as shown by the macrocytosis (volume index, 1.29) which indicates a deficiency of the specific maturing factor (EMF).

the blood stream; hence there is an excessive output of bilirubin, the end-product of hemoglobin destruction. The cells in the circulation are large and often of abnormal shape. If iron is lacking, the picture of the physiological process is exactly opposite (Fig. 17). Here, as the result of a lack of hemoglobin for the cell to carry, the mean cell volume is

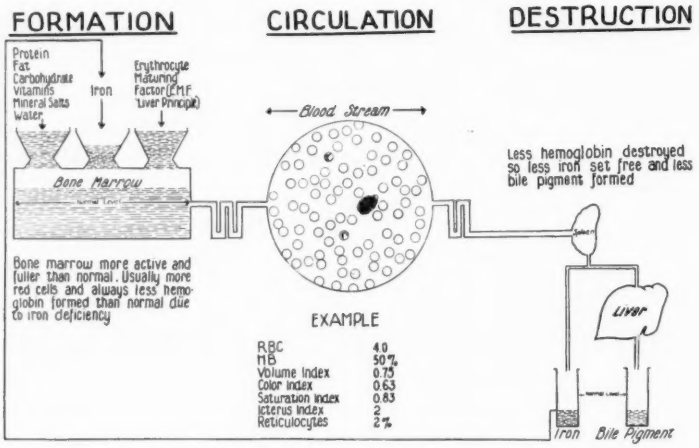


FIGURE 17: The red cells with a deficient intake of iron. As a result of the chronic iron deficiency, the hemoglobin is reduced (color index, 0.63) and the cells become smaller (volume index, 0.75). The icterus index is low because less hemoglobin than normal is discharged.

less than normal and the stroma is only partly filled with hemoglobin. As less hemoglobin is destroyed, the plasma is pale because of the low bilirubin content.

Summary

The great interest and importance of the erythrocyte has been emphasized in the preceding pages. The red corpuscle was the first cell seen by the human eye when the microscope unfolded a new world of minute things. Three of the five great early microscopists, Swammerdam, Malpighi, and Leeuwenhoek, independently discovered the red cell and found it an object of exceptional interest.

The structure of the red corpuscle has been determined accurately only recently. The balloon-like structure and the unusual surface membrane seem closely related to the peculiar biconcave shape. This discoidal form is readily altered chemically and physically by injurious agents and mechanical procedures. With injury, the shape tends to become spherical from the play of surface tension forces.

The red cell acts as a cup on an endless chain conveyor whose function is to ferry oxygen from the lungs to the tissues. It is so small that about 60,000 can be placed on the head of a common pin. Each cell makes about 60,000 round trips from lungs to tissues during the average lifetime of thirty days.

All the cells together, the erythron, constitute a vessel for holding hemoglobin by which the oxygen is carried.

The normal red cell is a biconcave disk. There may be congenital variations in shape and structure. Spherocytosis and ovalocytosis are anatomic variations in shape. With certain congenital abnormalities of structure, the cell may become sickle shaped under certain conditions as in sickle-cell anemia, or be destroyed more easily than normal as in Mediterranean (Cooley's) anemia.

All measurements of the red cell are easily made and are of great clinical significance. With accurate measurements the exact total mass of cells in the body is known and the configuration of the mean erythrocyte, the unit of the erythron, can be visualized.

From the laboratory standpoint, the anemias are best classified on the basis of the volume and hemoglobin content of the mean red cell. Such measurements often give a clue to the etiology of the anemia.

With a study of the red cell and bilirubin, the end-product of hemoglobin metabolism, the physiology of the red cell can be determined in any given case.

The treatment of anemias due to a deficiency of the erythrocyte-maturing factor (EMF) of liver, and those due to a lack of iron, is best gauged by a careful study of the mean red cell. If the elements deficient are properly supplied, the cells return to normal.

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